Development

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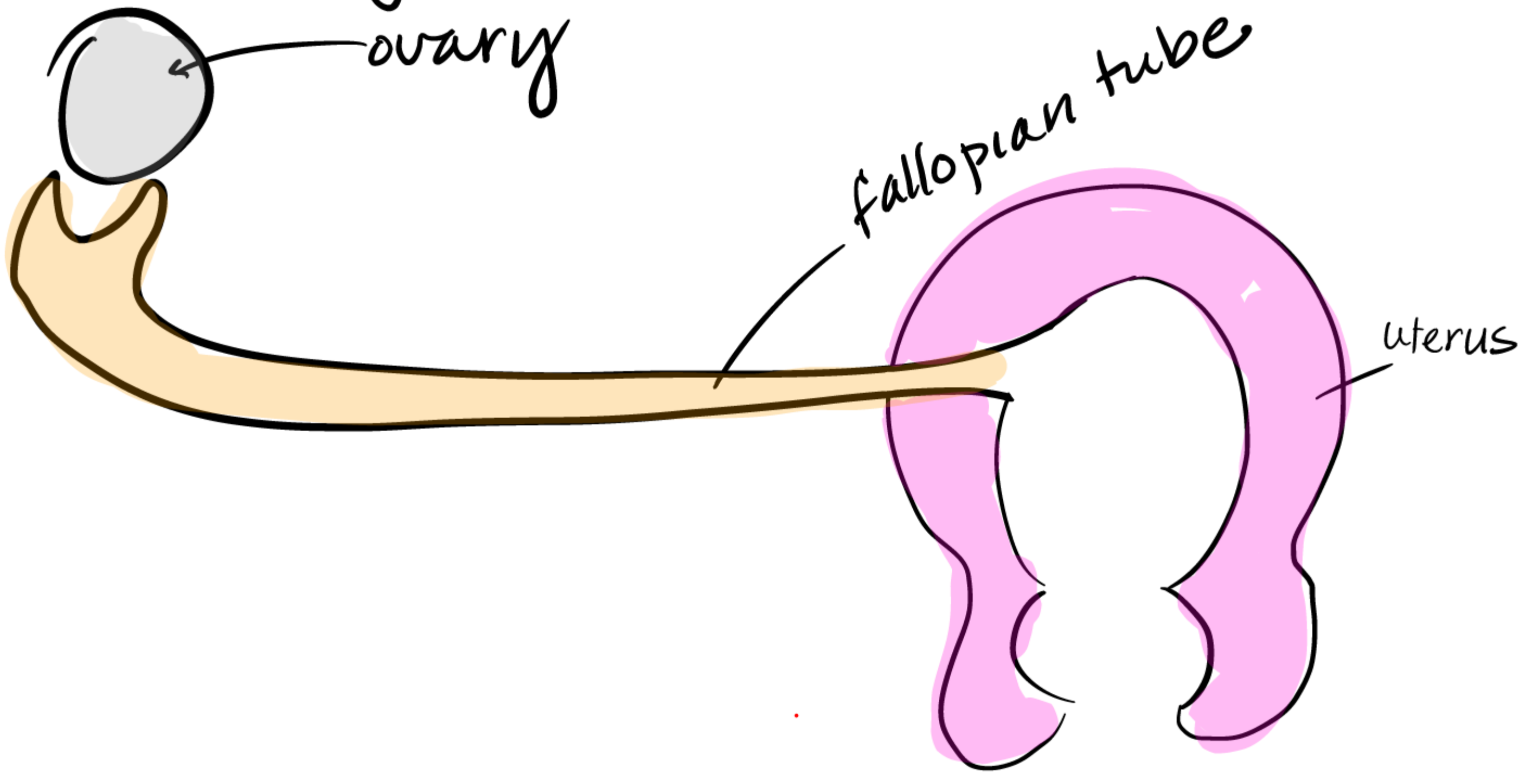
Introduction

- Operation of the brain – why it is important to get it right!
  - Precise interconnections among 100 billion neurons
- Brain development
  - Begins as a tube
  - Neurogenesis, synaptogenesis, pathway formation, connections formed and modified
- Wiring in brain
  - Establishing correct pathways and targets
  - Fine tuning based on experience

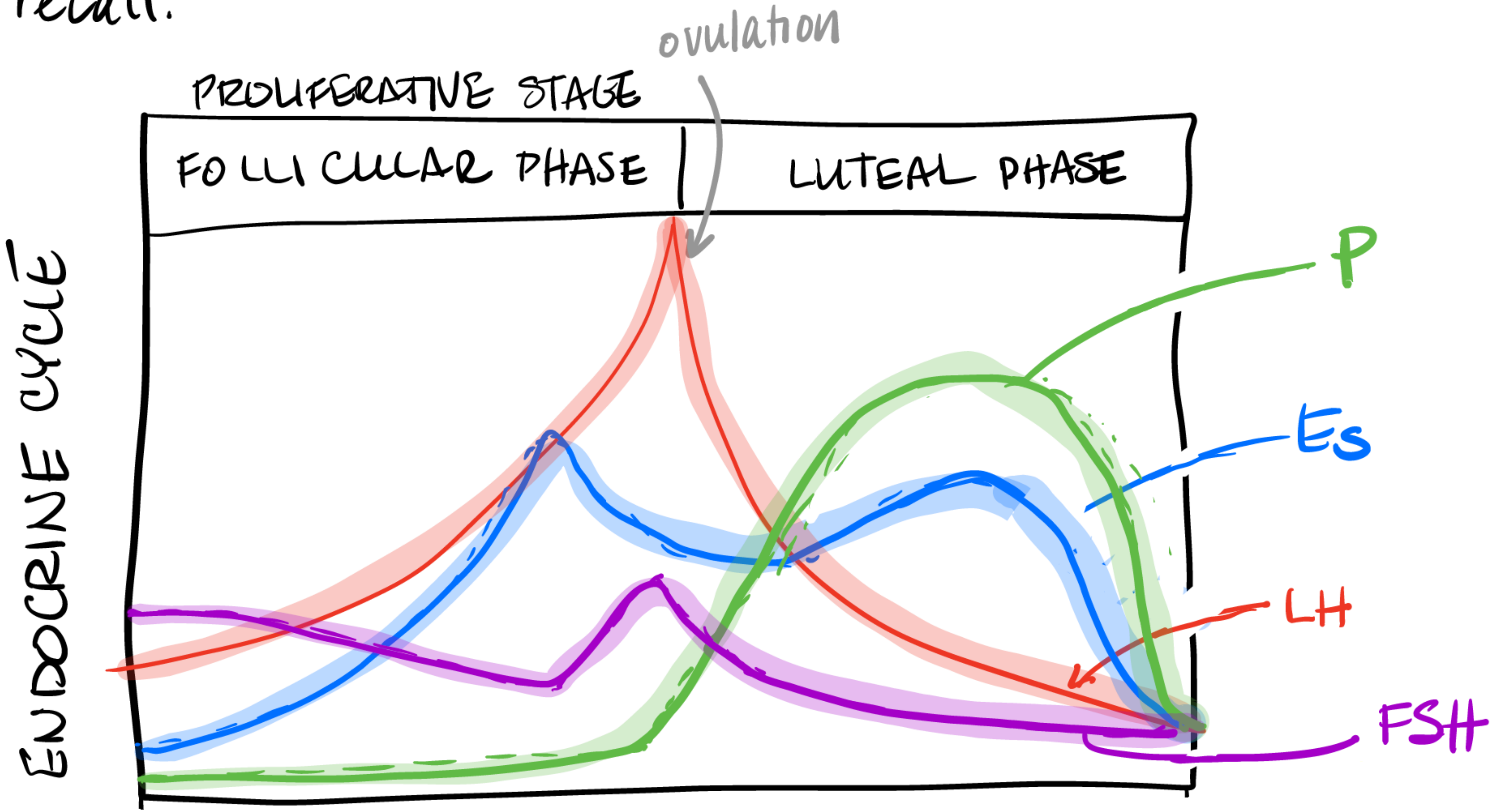
Development of the Nervous System

↳ the art of learning complex things
is to take it slowly - step by step ☺
- on the basics -

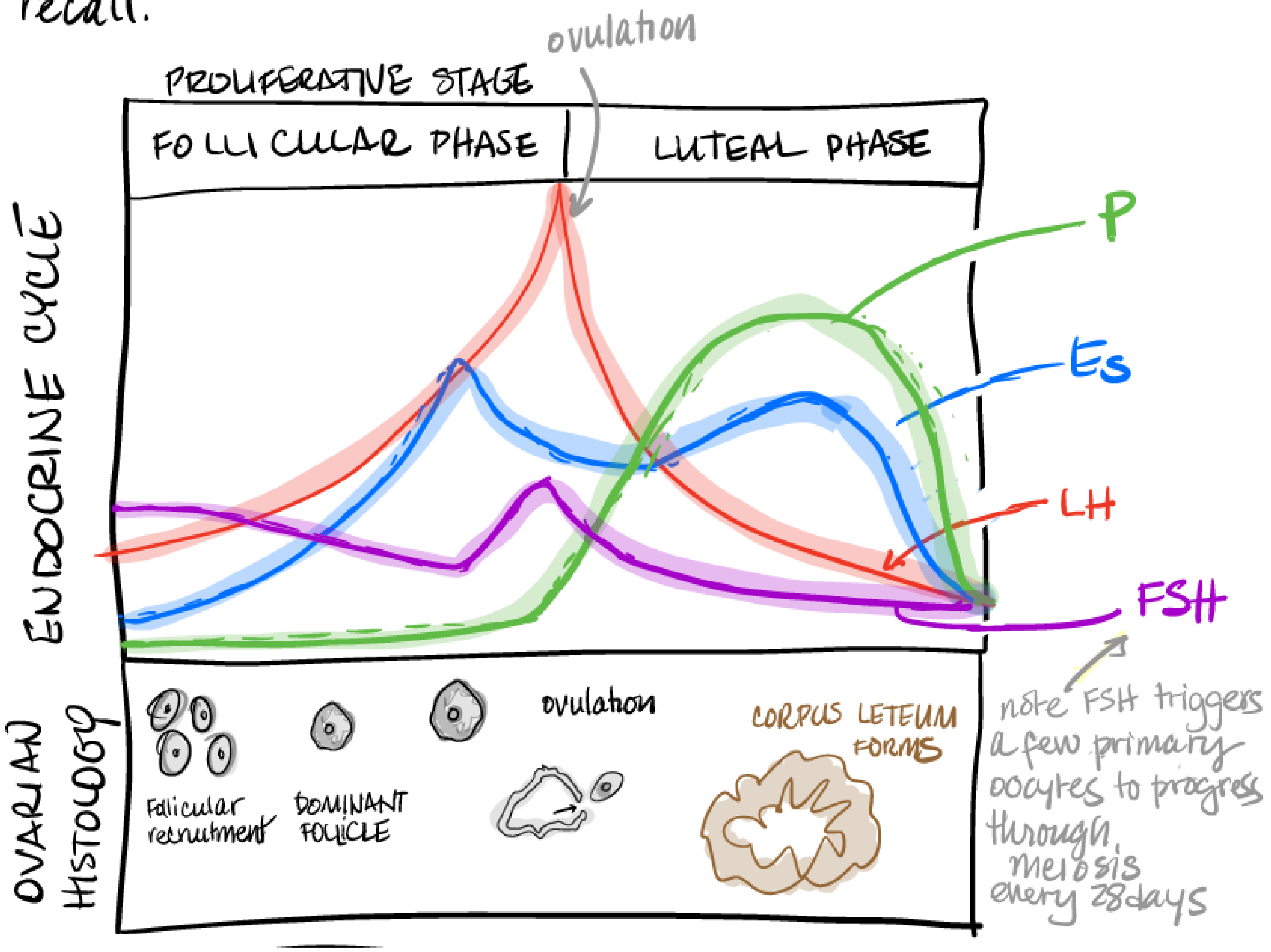
↳ in the begining...



recall:

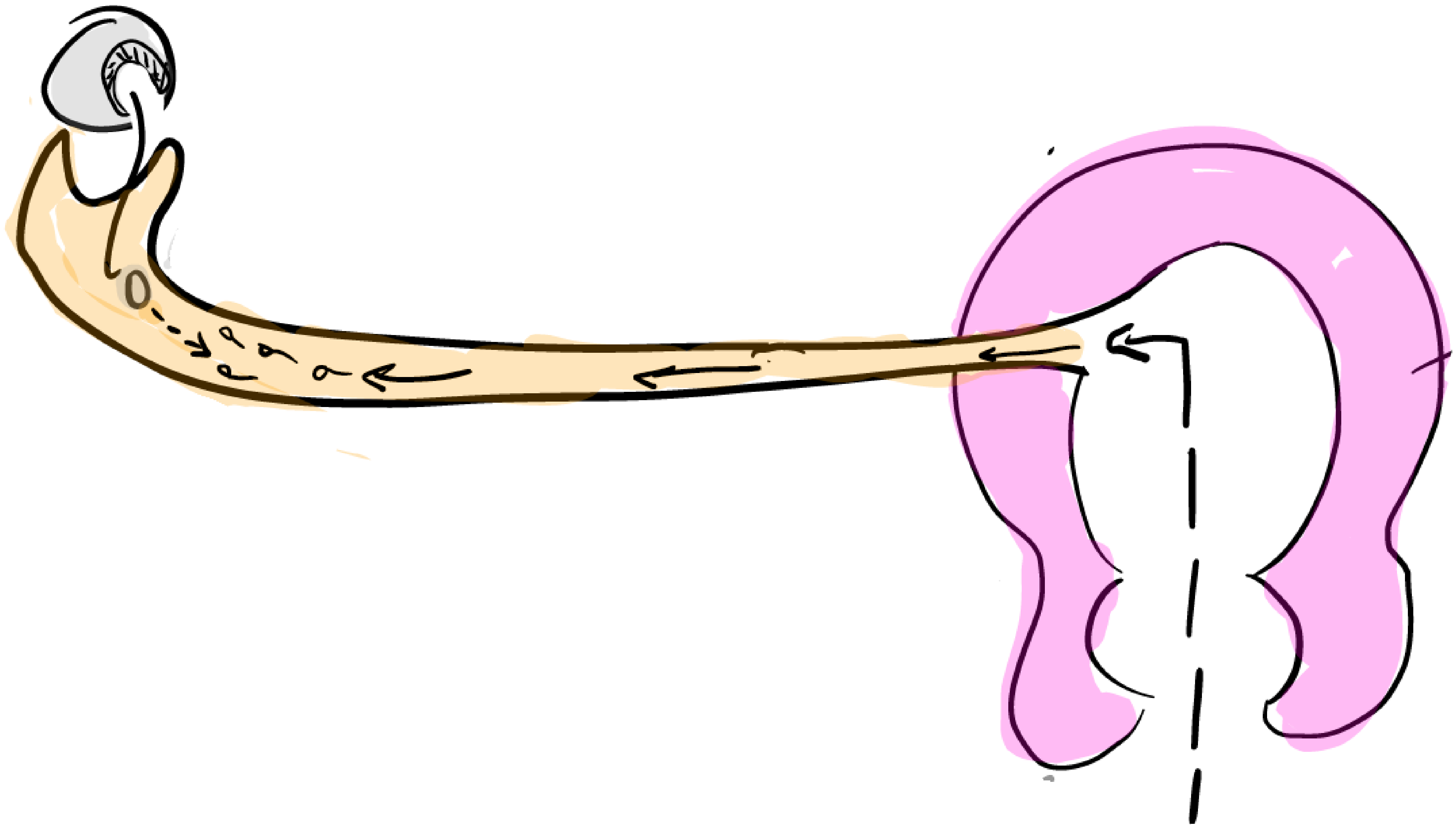

ovulation
PROLIFERATIVE STAGE
FOLLICULAR PHASE
LUTEAL PHASE
ENDOCRINE CYCLE
P
Es
LH
FSH

recall:

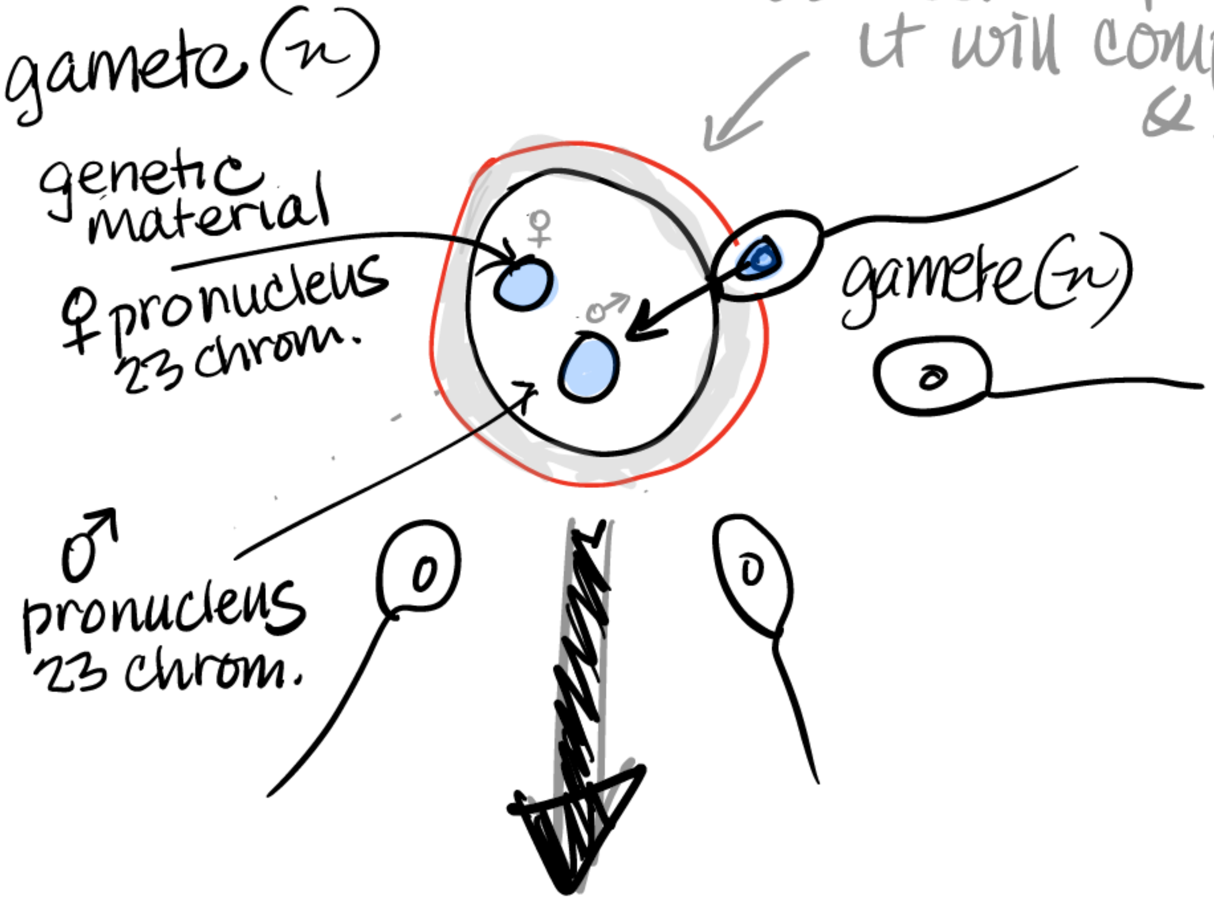


ovulation
PROLIFERATIVE STAGE
FOLLICULAR PHASE
LUTEAL PHASE
ENDOCRINE CYCLE
P
Es
LH
FSH
OVARIAN HISTOLOGY
follicular recruitment
DOMINANT FOLLICLE
ovulation
CORPUS LETEUM FORMS
note FSH triggers a few primary oocytes to progress through meiosis every 28days

DAY 14




released
DAY 14
Fertilised
ovum



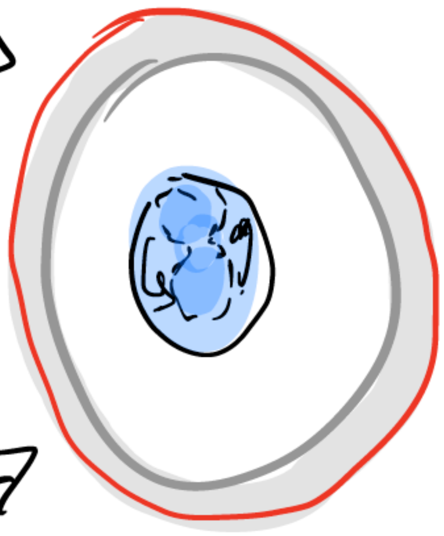
as soon a sperm contacts ovum, it will complete 2nd mitotic division & finish metaphase II & release 1 more polar body & become "DIFINITIVE OVUM" zygote (2n)

pronuclei fuse ⇒ diploid cell (46 chromosomes)

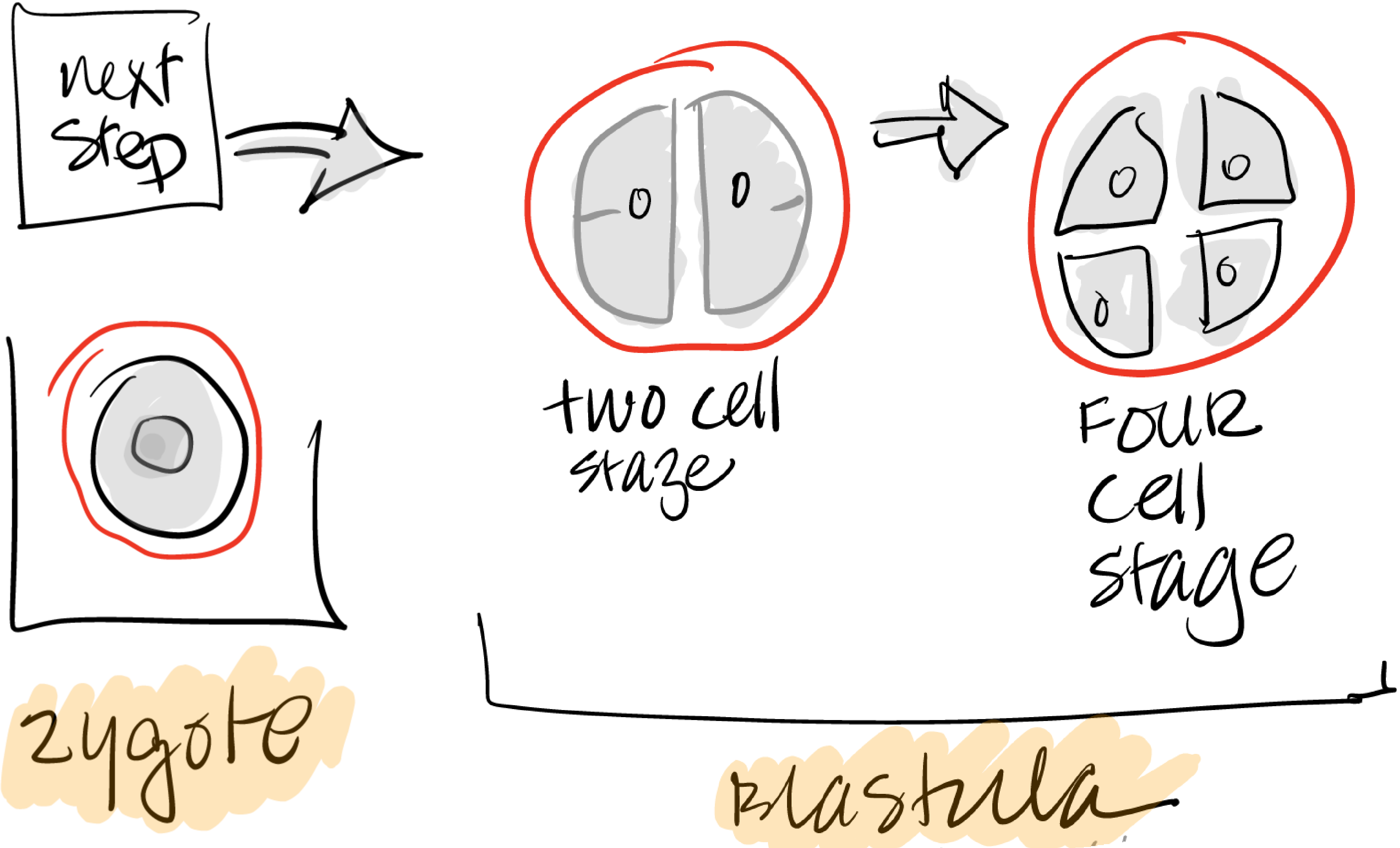
↳ once it has 46 chromoses the cell will plan to divide

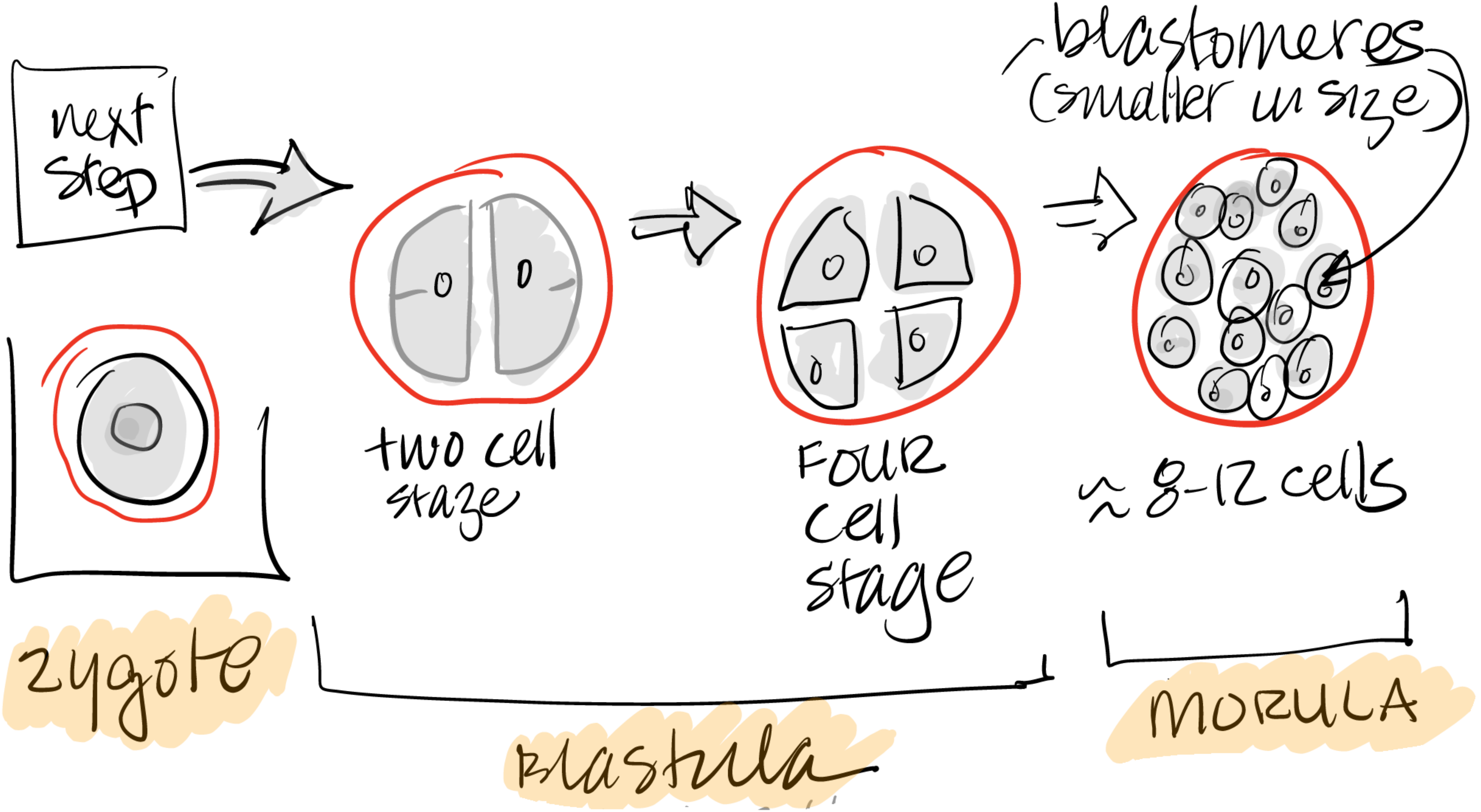
↳ "no intention to die b/c it has rec'd a sperm

↳ it will now plan to multiply"

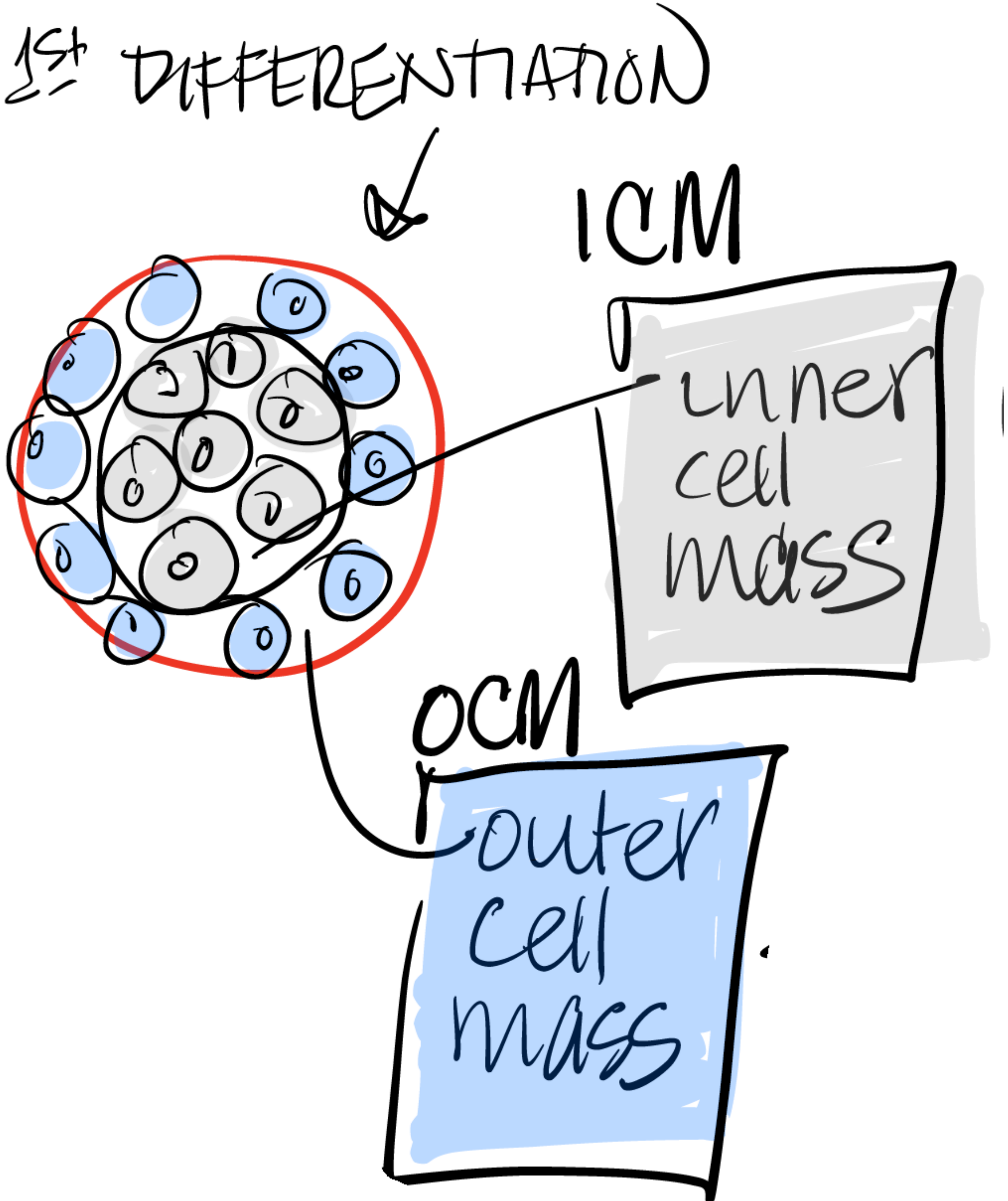


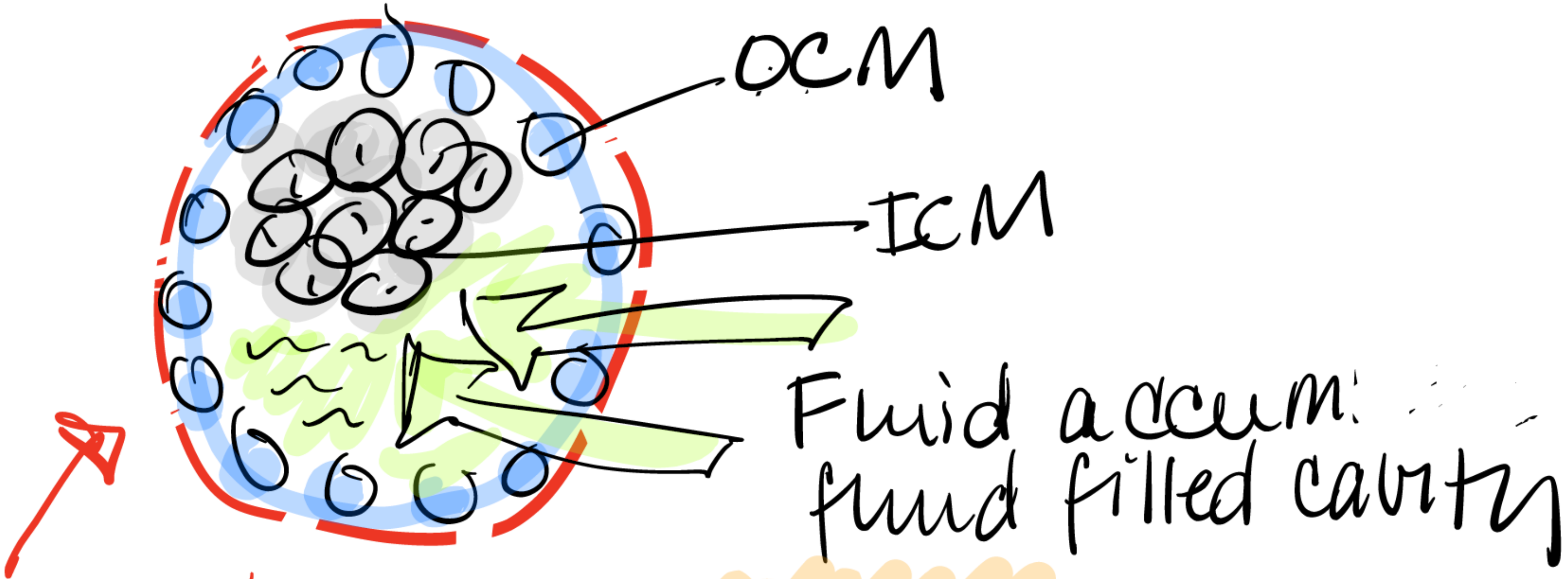
note zona pellucida is still present


next step
zygote
two cell stage
four cell stage
Blastula



next step
zygote
two cell stage
Four cell stage
blastomeres (smaller in size)
~ 8-12 cells
Blastula
MORULA

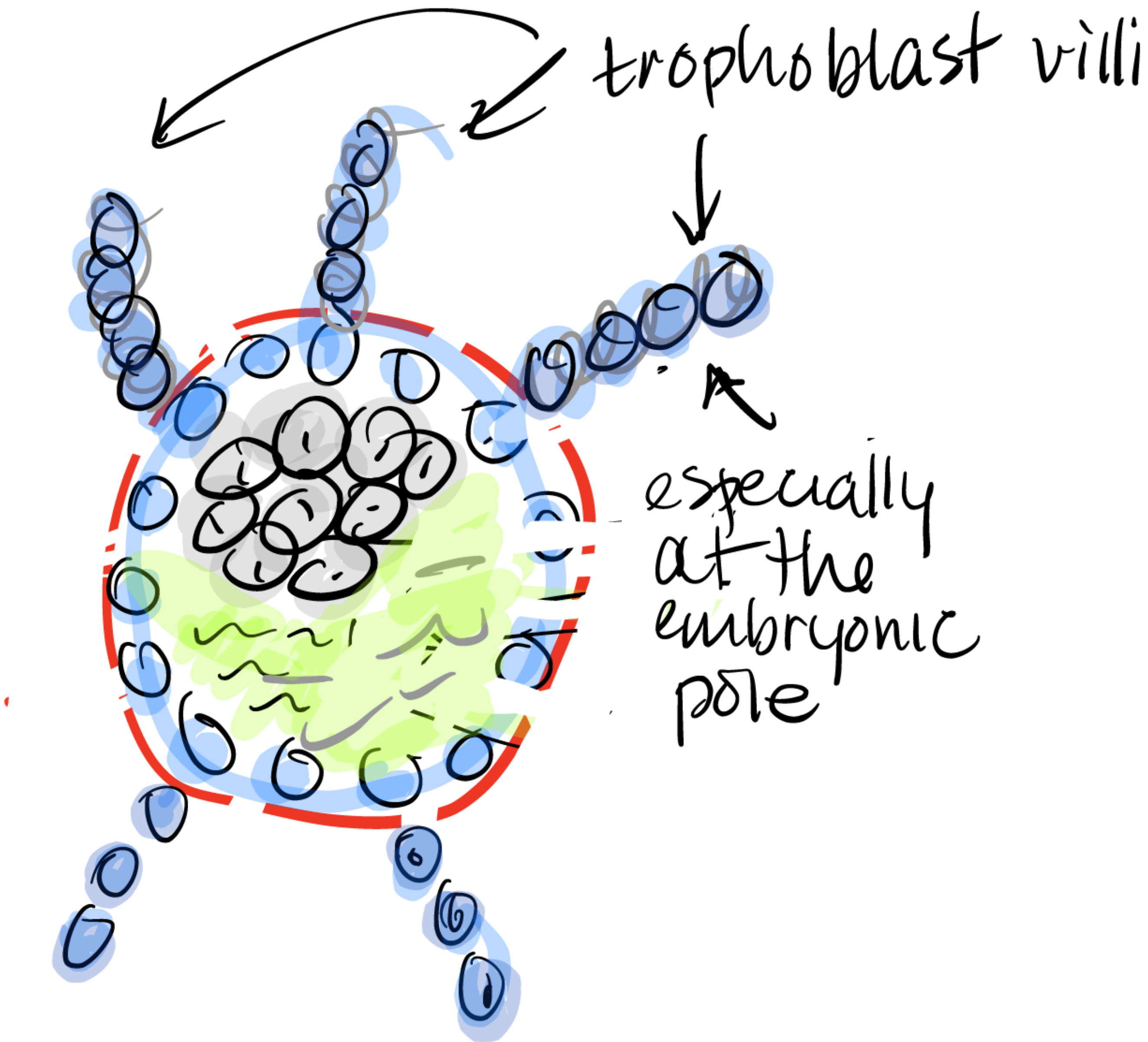

1st DIFFERENTIATION
ICM
inner cell mass
OCM
outer cell mass



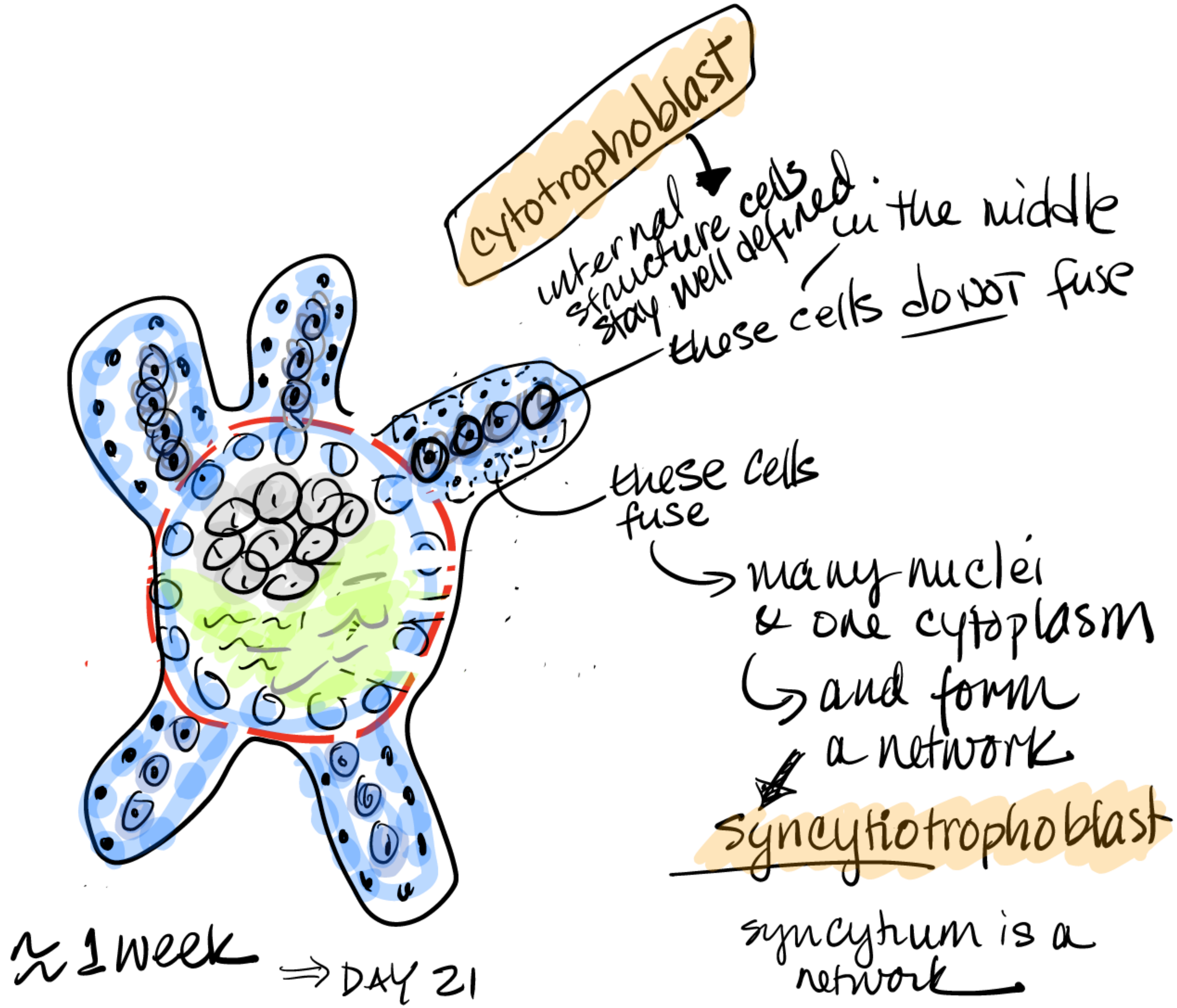
BLASTOCYST

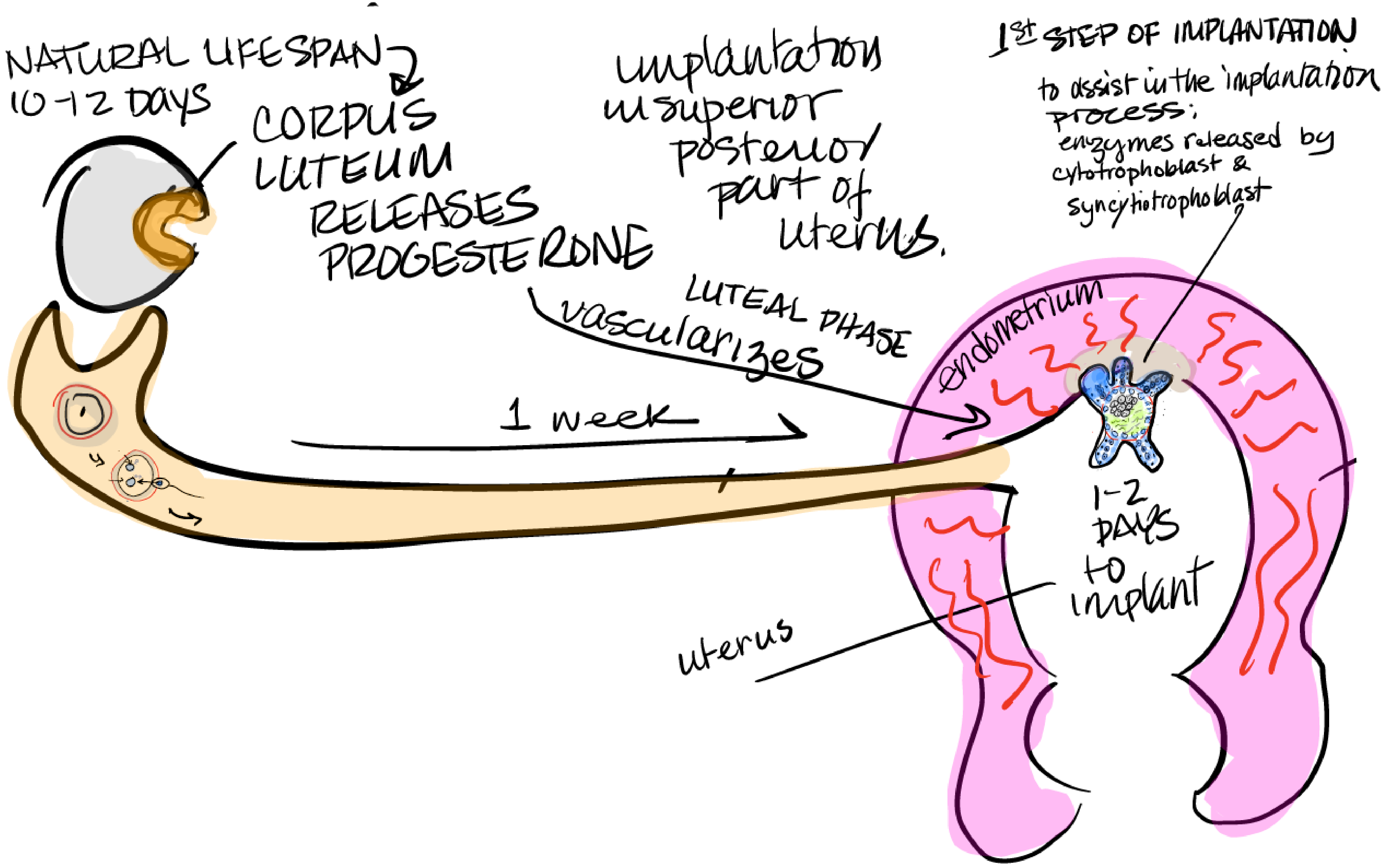
zona pellucida starts to dissolve
dissolution process

↪ this process is called "hatching"

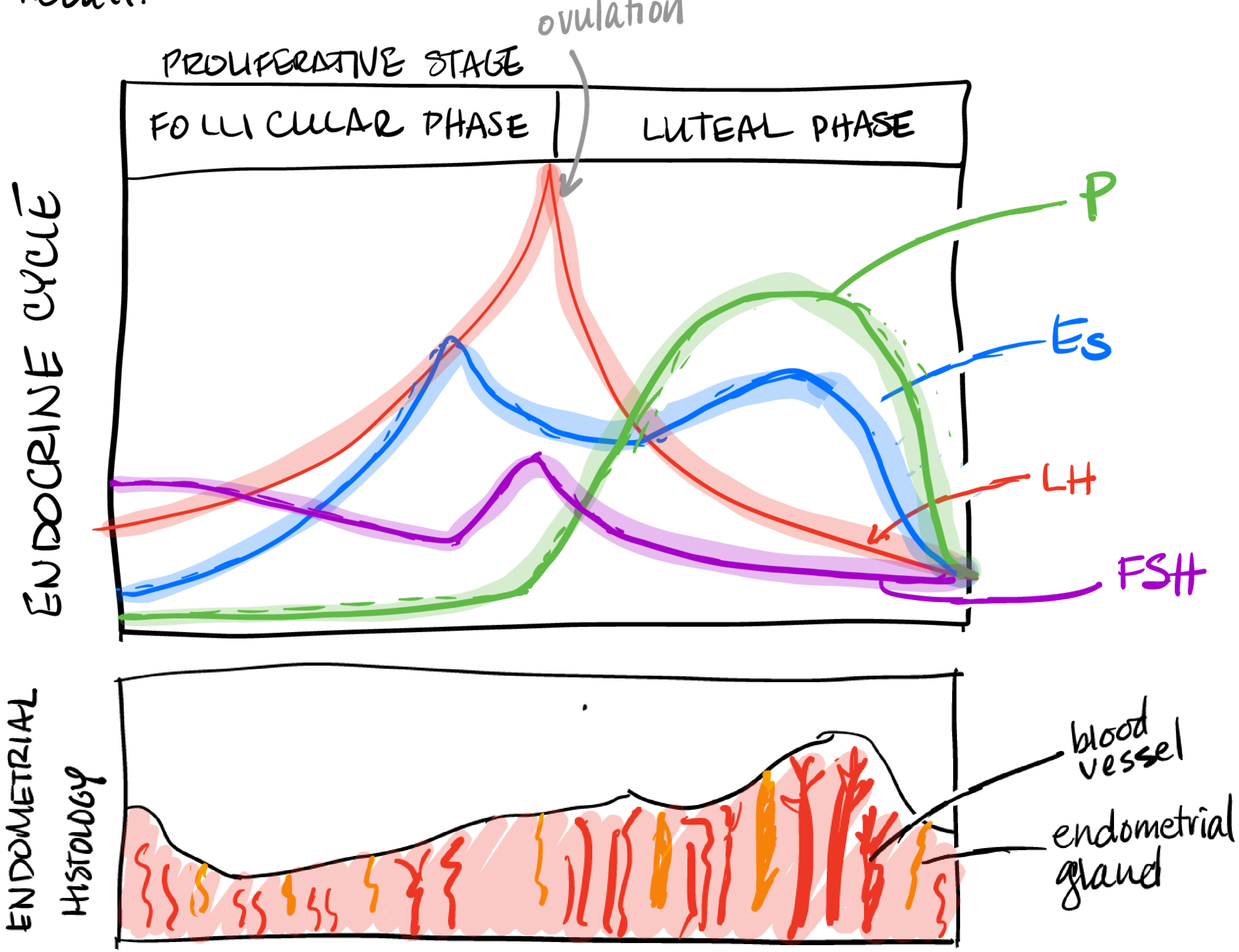


trophoblast villi
especially
at the
embryonic
pole


cytotrophoblast
internal structure cells stay well defined
in the middle
these cells do NOT fuse
these cells fuse
many nuclei & one cytoplasm
and form a network
syncytiotrophoblast
syncytium is a network
≈ 1 week
⇒ DAY 21

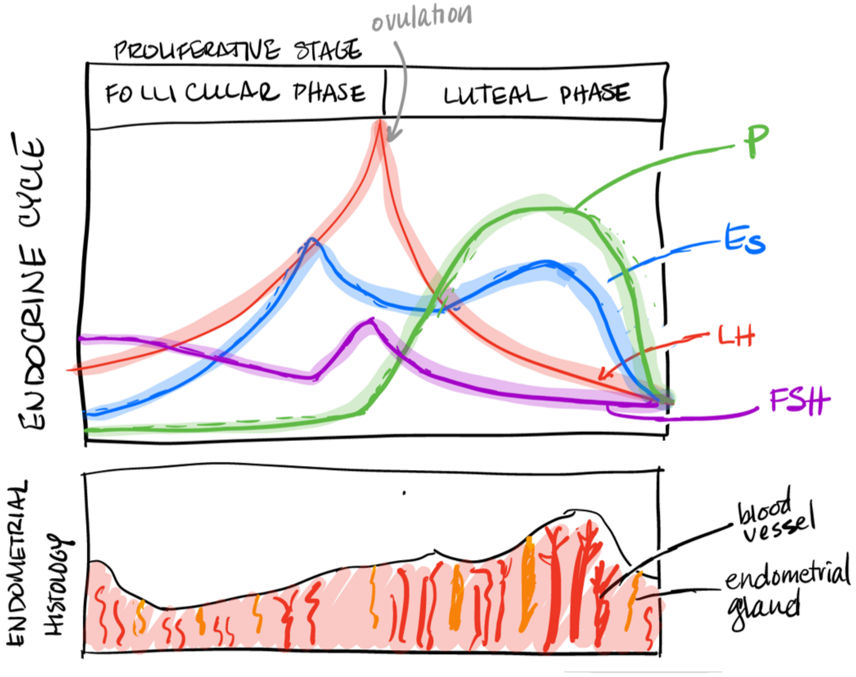

NATURAL LIFESPAN
10-12 DAYS
CORPUS LUTEUM RELEASES PROGESTERONE
implantation in superior posterior part of uterus.
1st STEP OF IMPLANTATION
to assist in the implantation process:
enzymes released by cytotrophoblast & syncytiotrophoblast
LUTEAL PHASE
vascularizes
endometrium
1 week
1-2 DAYS to implant
uterus

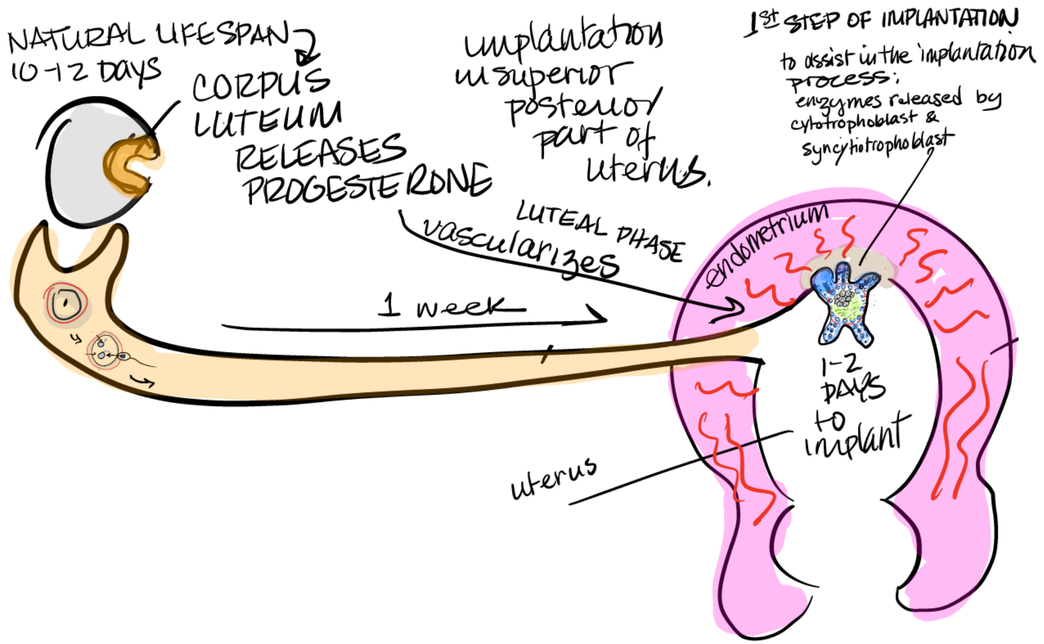
recall:


ovulation
PROLIFERATIVE STAGE
FOLLICULAR PHASE
LUTEAL PHASE
ENDOCRINE CYCLE
P
Es
LH
FSH
ENDOMETRIAL HISTOLOGY
blood vessel
endometrial gland

corpus luteum
↳ after 12 days
↳ dissolves

supply progesterone for 12 days
↳ when this happens the endrometrial vasularization ↓ and bleeding begins
↳ menstrual bleeding





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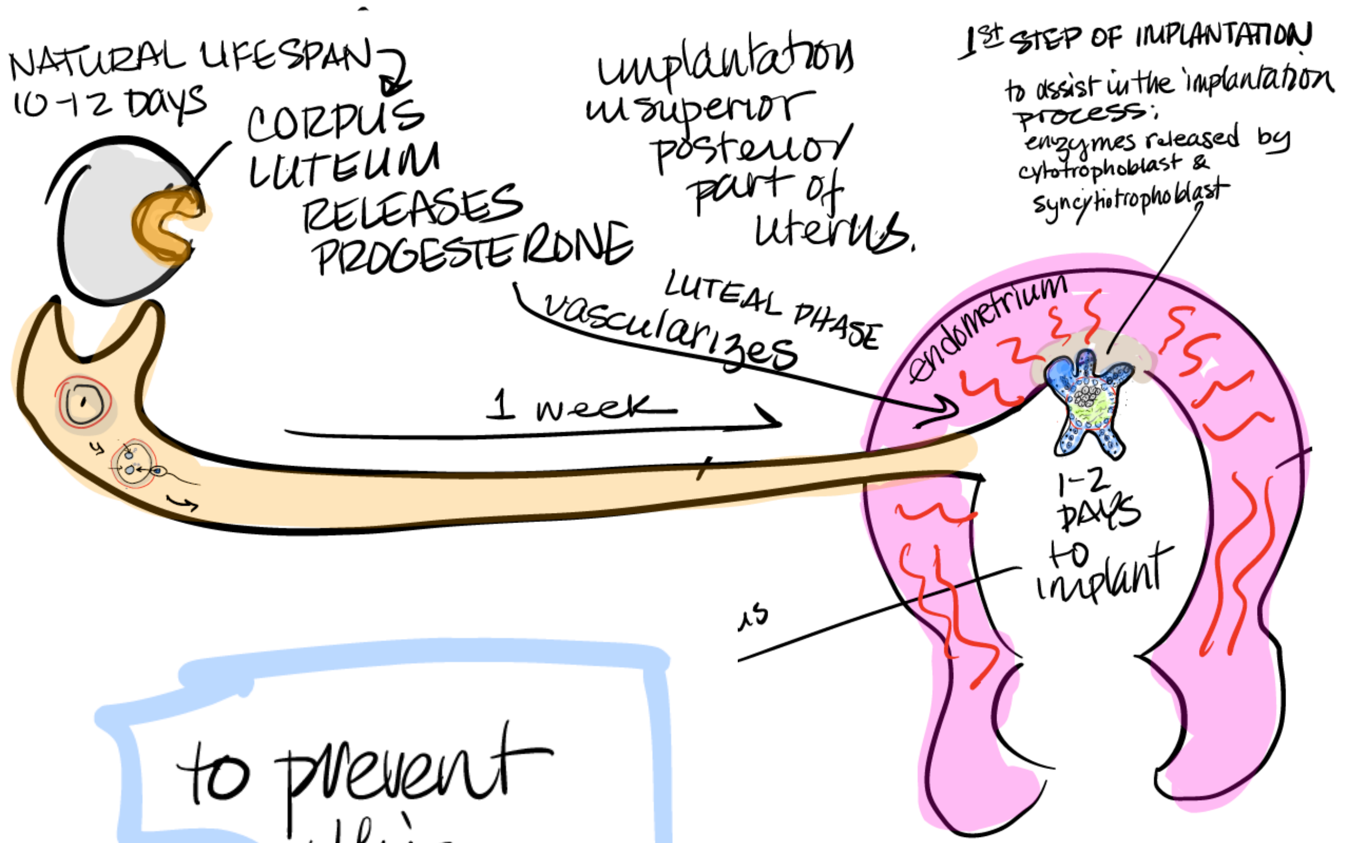
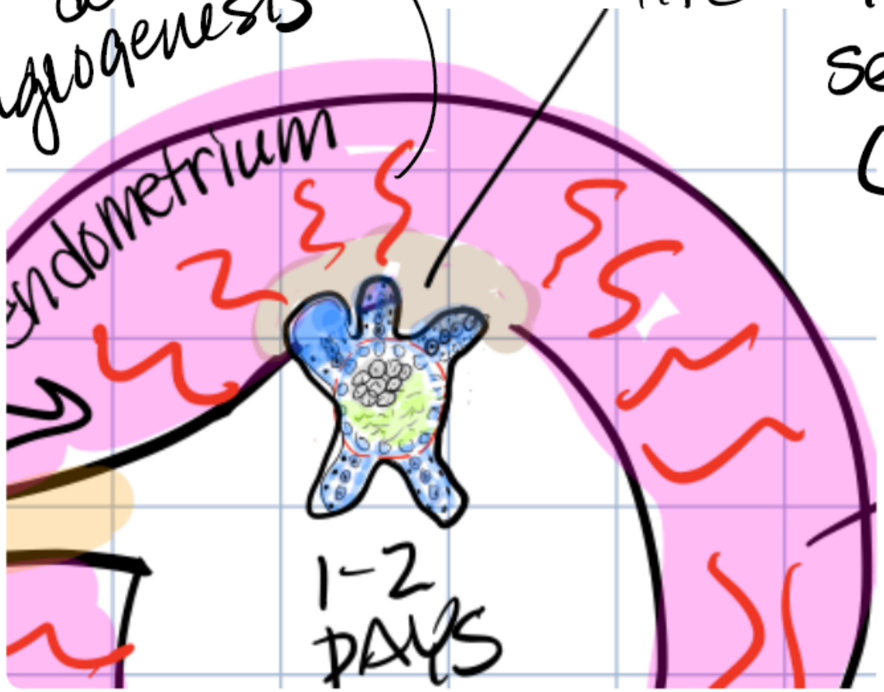


to prevent this the cytotrophoblasts secrete hCG



THE syncytiotrophoblasts
CYTOTROPHOBLASTS
secrete hCG
(human
Chorionic
Gonadotropin)
(week 2)

⇓

Fusion of
trophoblast
&
endometrium

hCG + pregnancy test

→ hCG will inform the corpus luteum the "good news" that the ovum you released has met w/ a sperm & implanted itself in the uterus.

→ & please don't degenerate

→ now corpus Luteum will grow rapidly & become

corpus GRAVIDARUM

with hCG from cytotrophoblasts

corpus luteum grows into

⇓

corpus gravidarum

(Luteotropic effect)

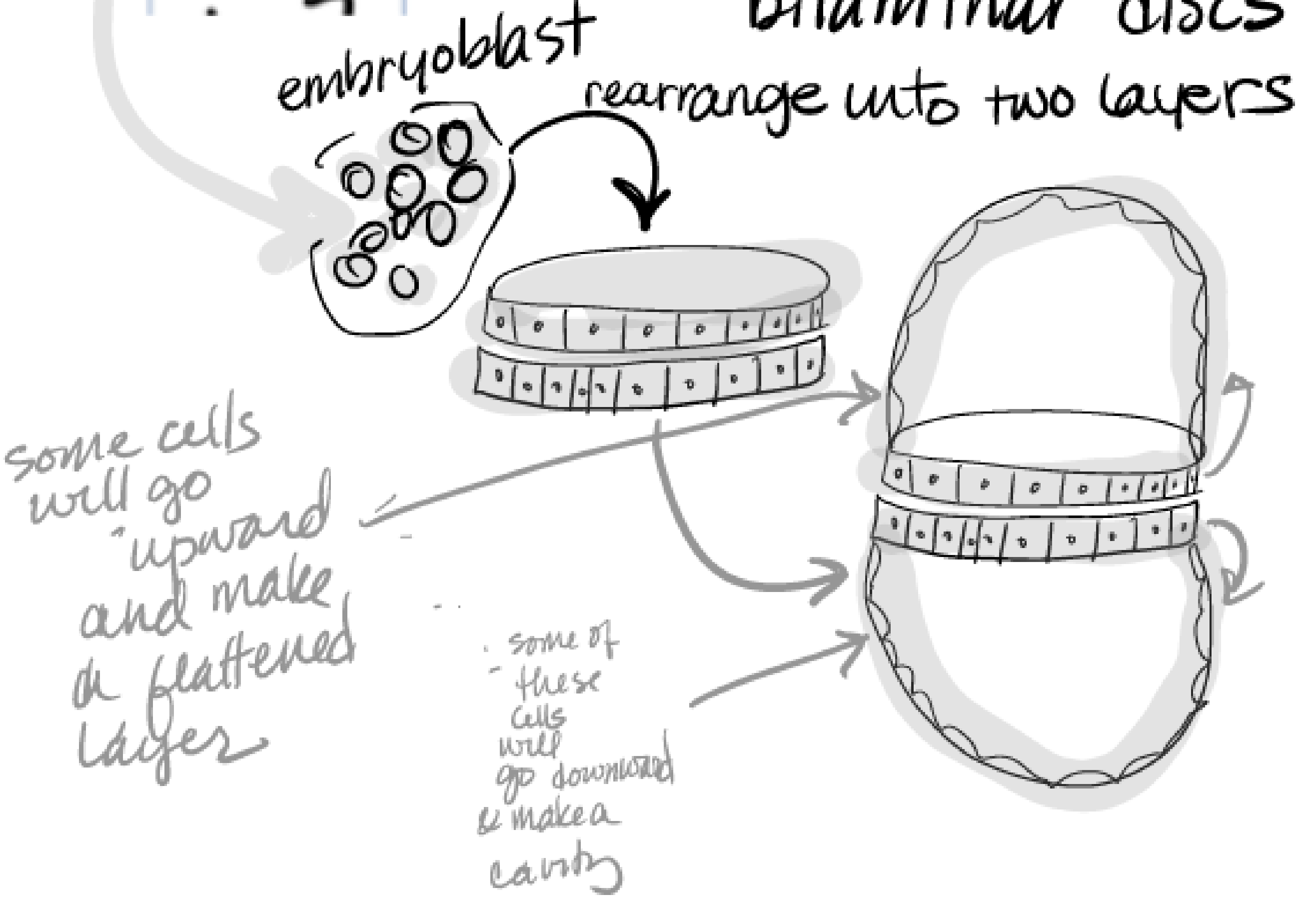
↑↑ progesterone

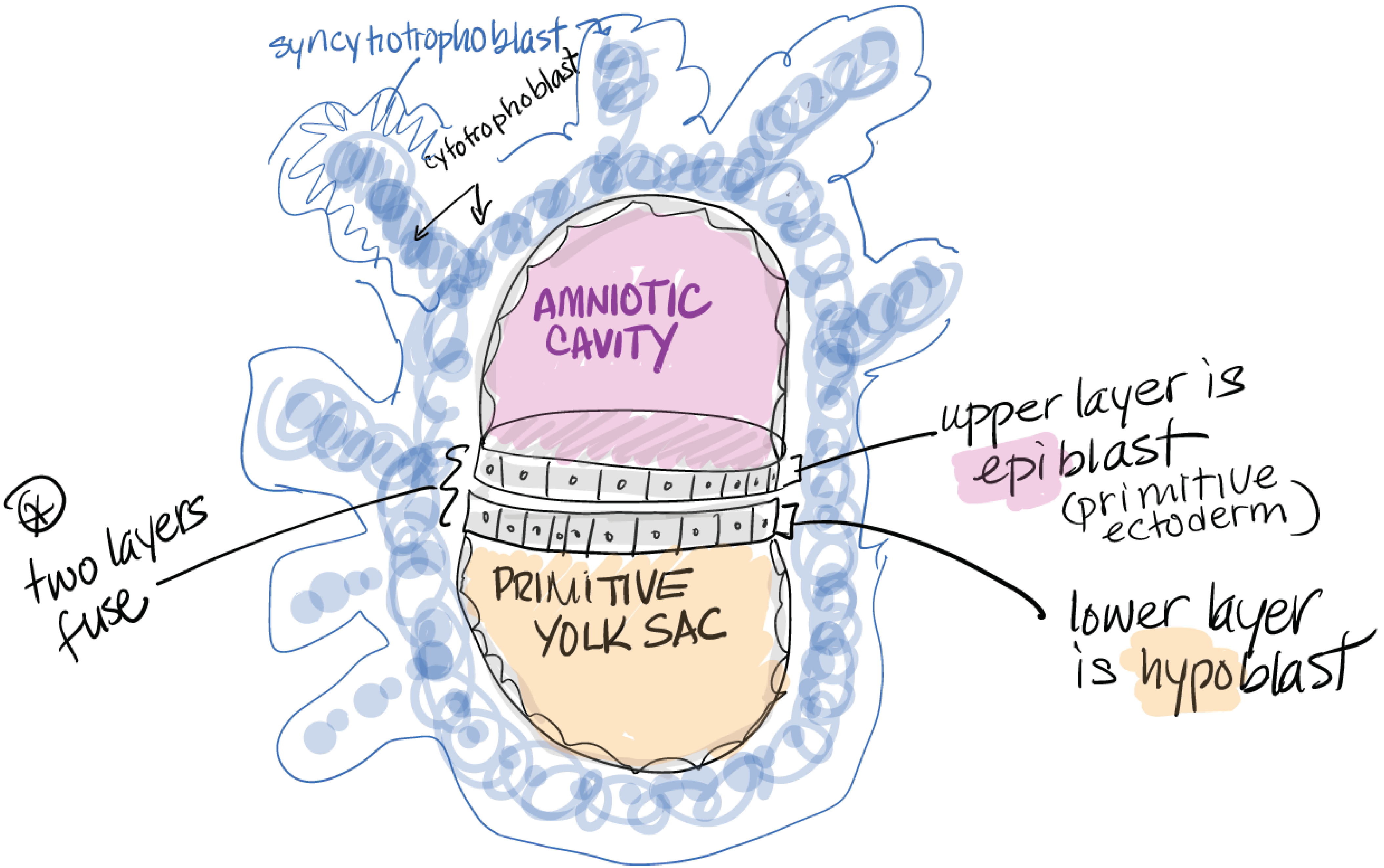
* to keep endometrium intact

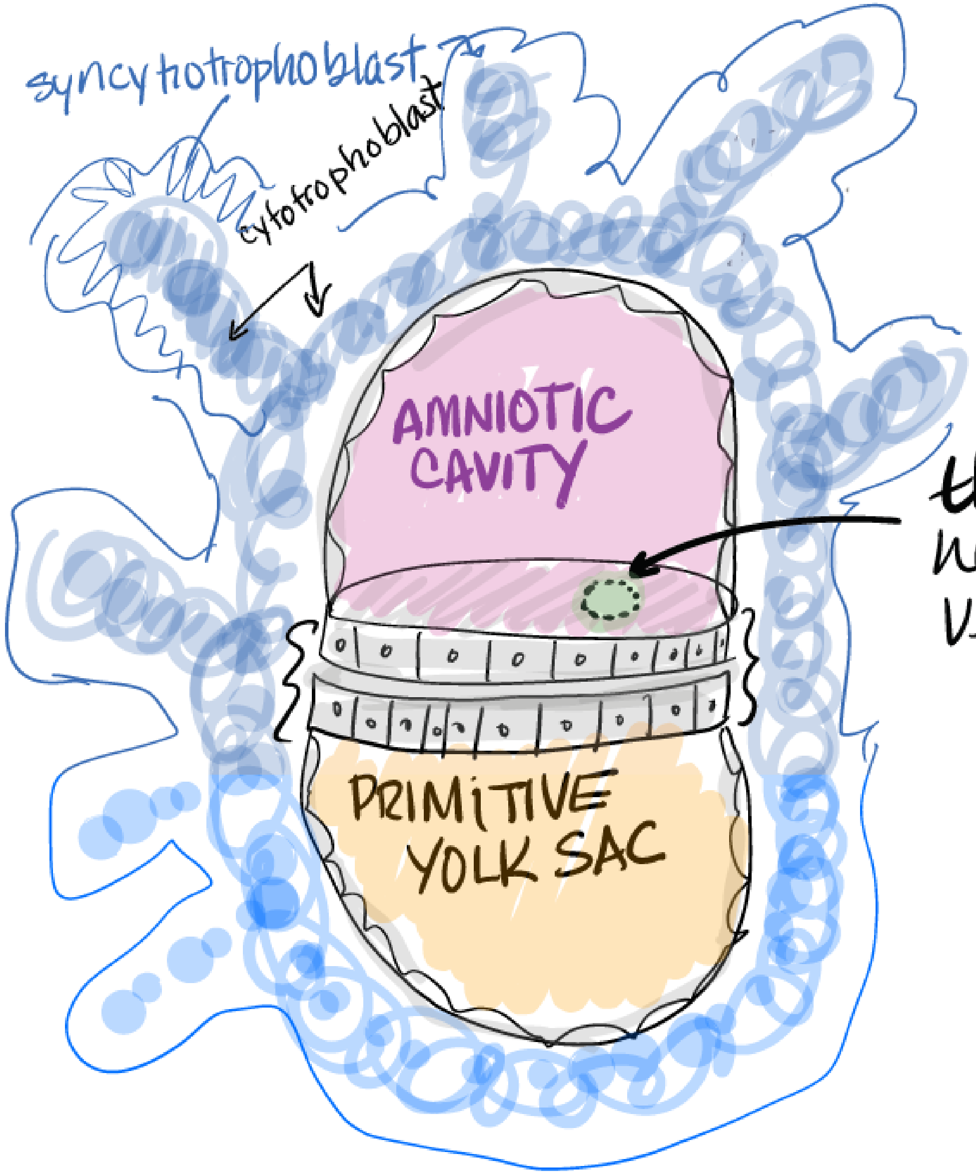
Week 2 of Development

① Development of BILAMINAR DISC

embryoblast separately proliferates and then they are converted into two bilaminar discs.




syncytiotrophoblast
cytotrophoblast
AMNIOTIC CAVITY
upper layer is epiblast (primitive ectoderm)
two layers fuse
PRIMITIVE YOLK SAC
lower layer is hypoblast

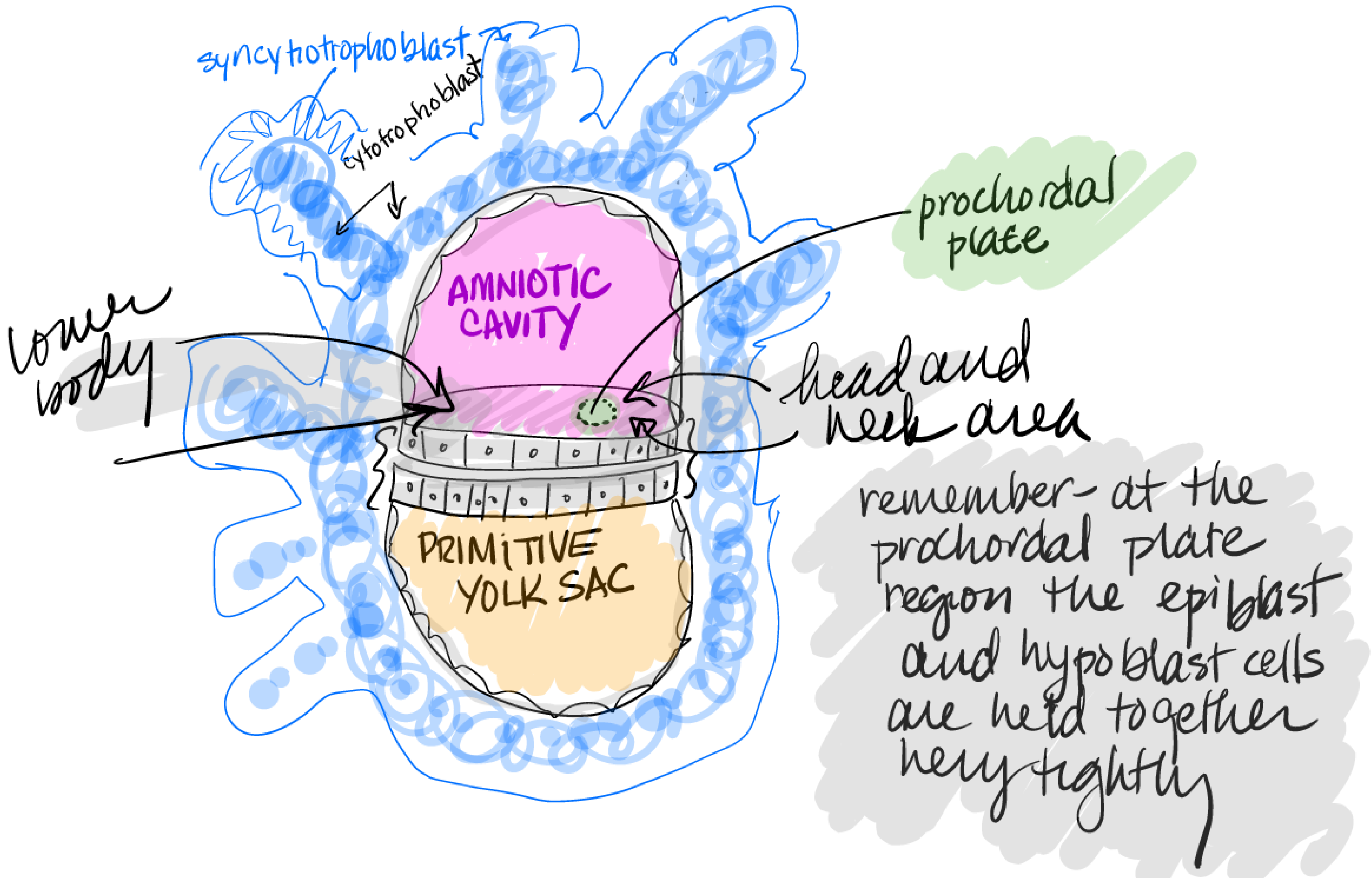


the PROCHORDAL PLATE

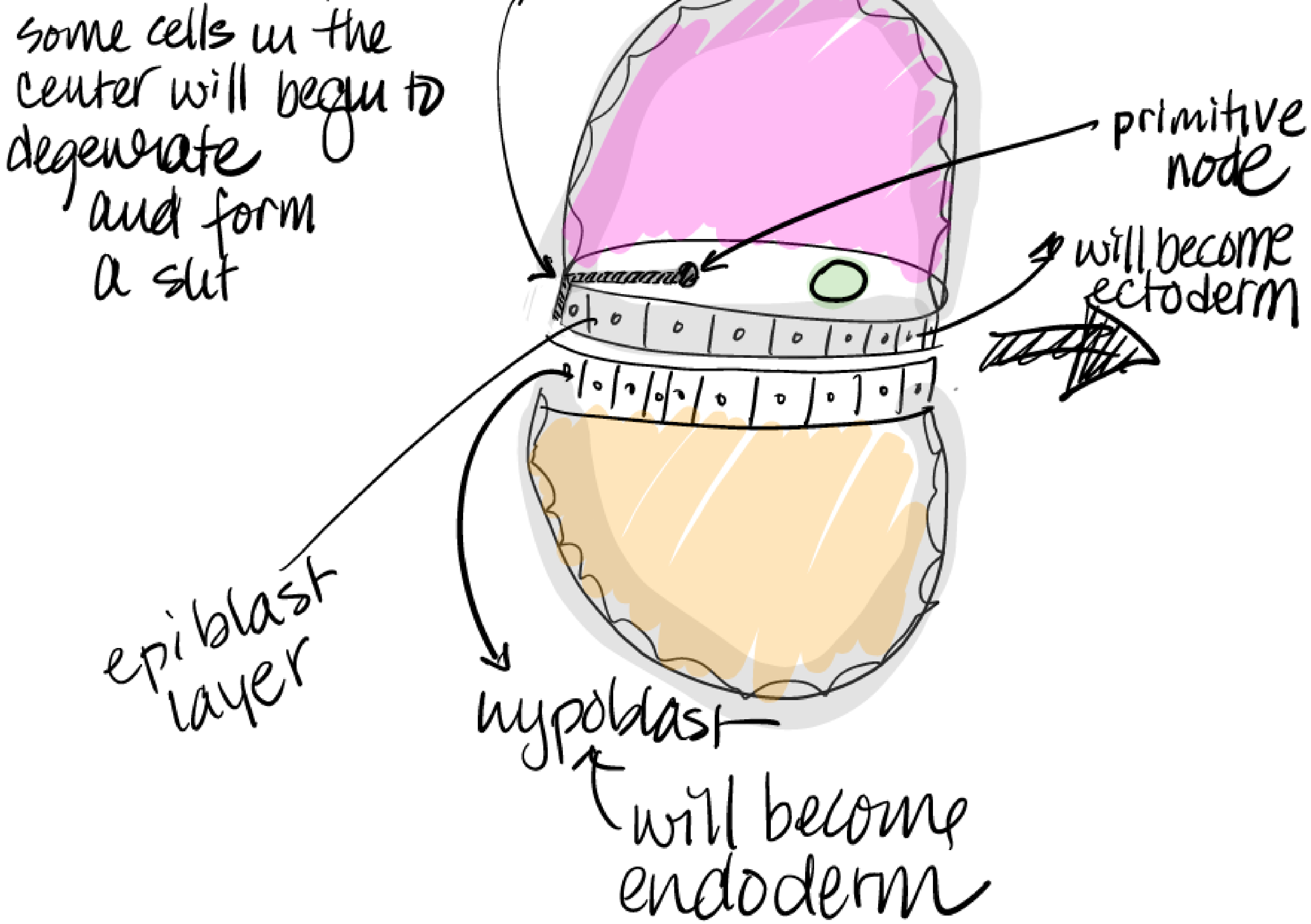
these cells are held together very tightly

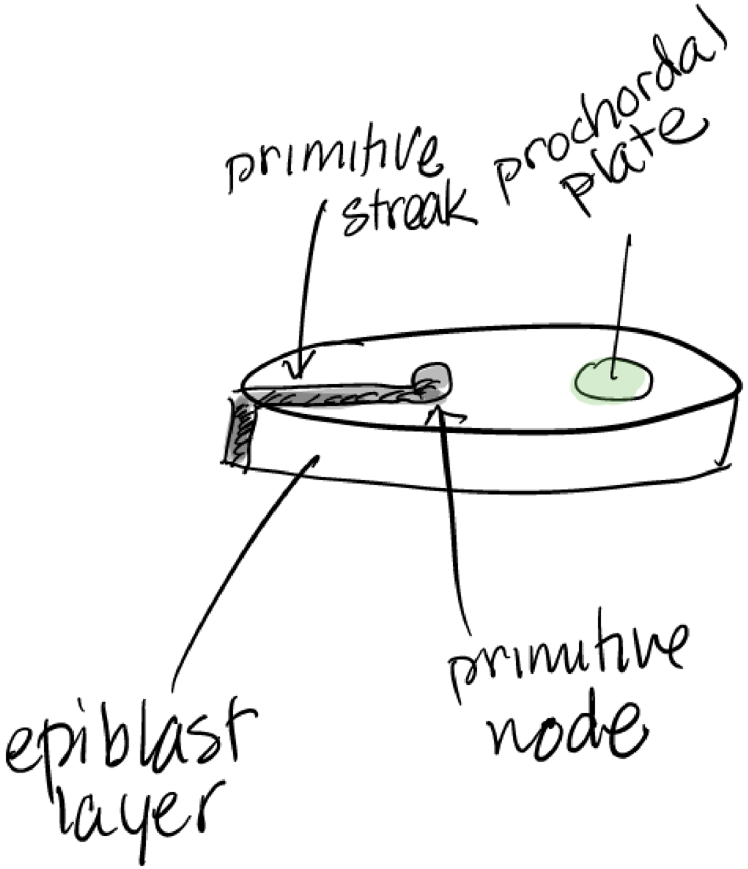
future mouth

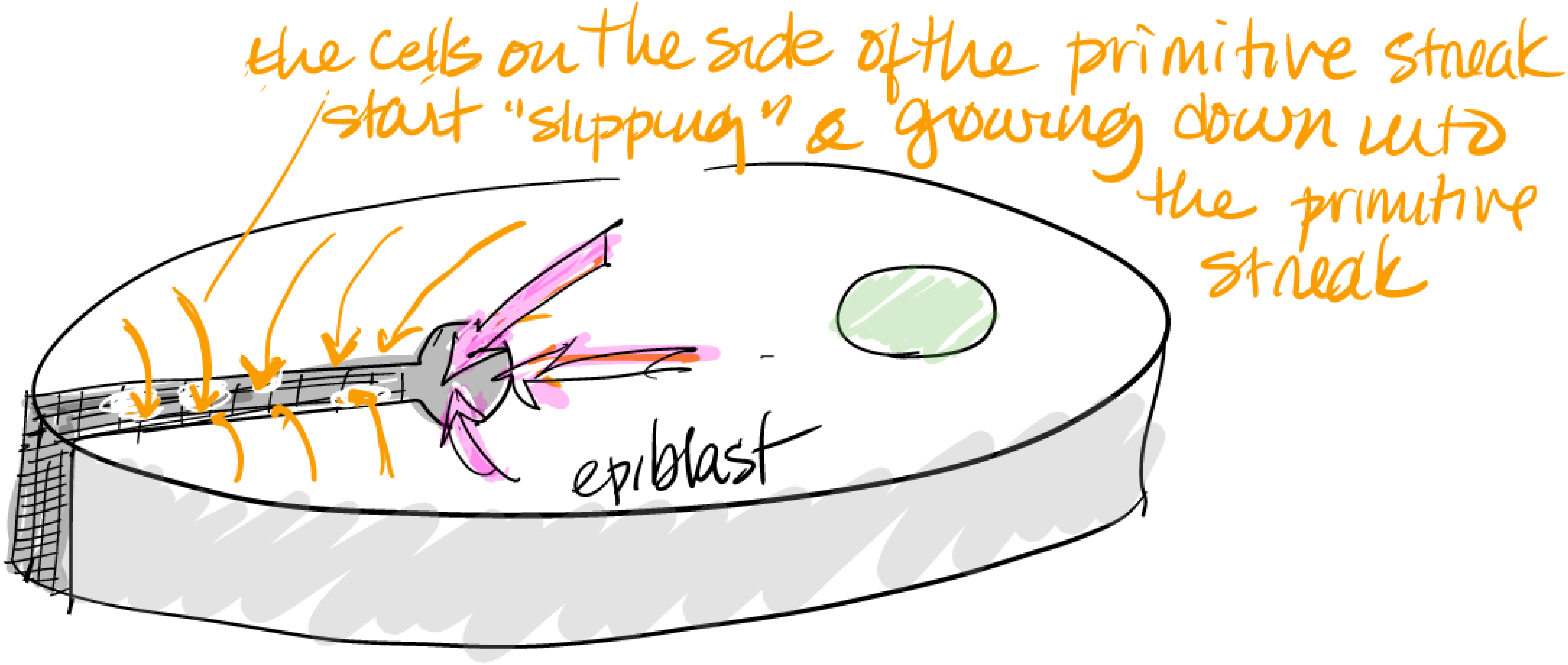
→ this prochordal plate now determines which is the cephalic area & which is caudal

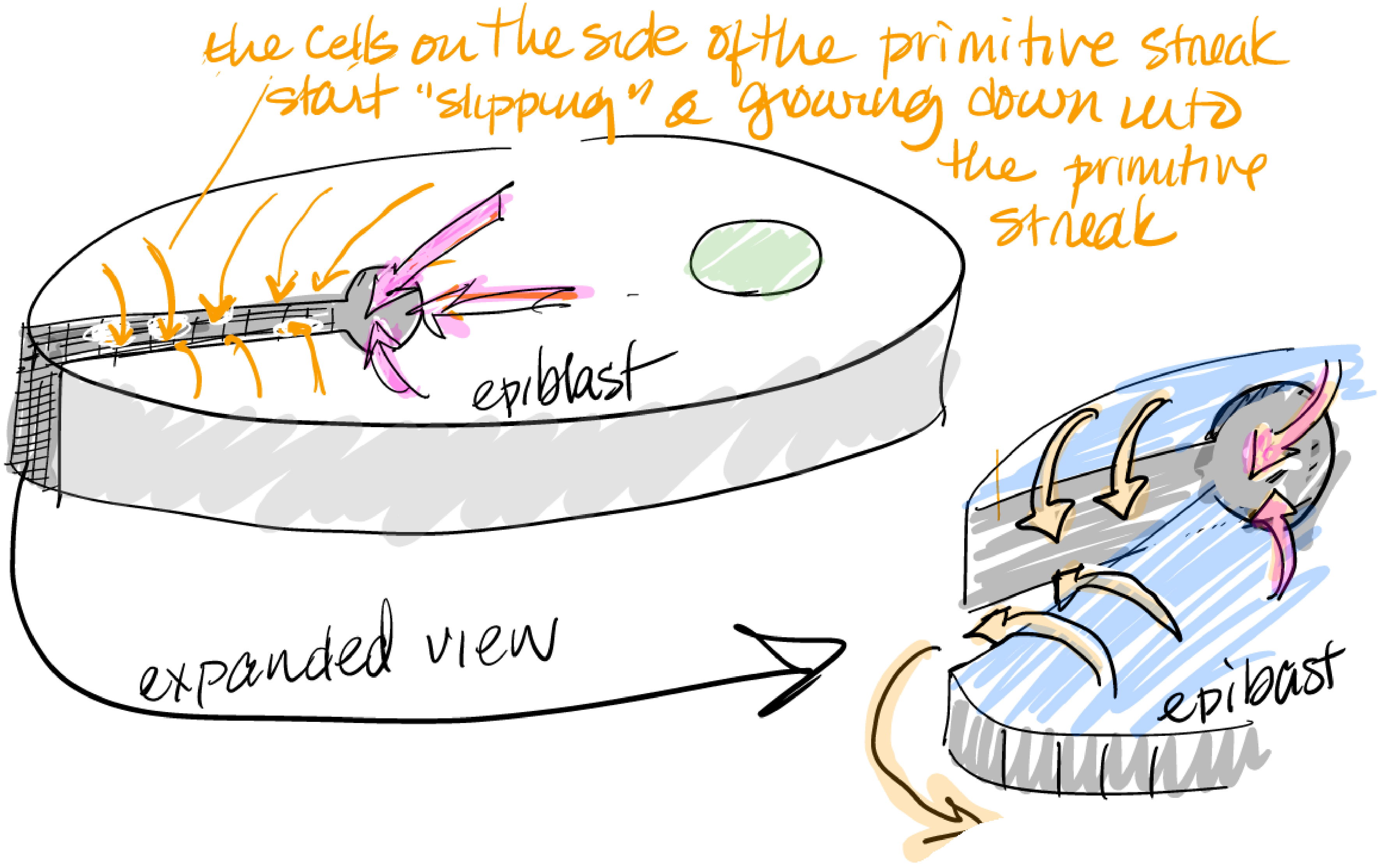

syncytiotrophoblast
cytotrophoblast
prochordal plate
AMNIOTIC CAVITY
lower body
head and neck area
PRIMITIVE YOLK SAC
remember- at the prochordal plate region the epiblast and hypoblast cells are held together very tightly

Development of primitive streak



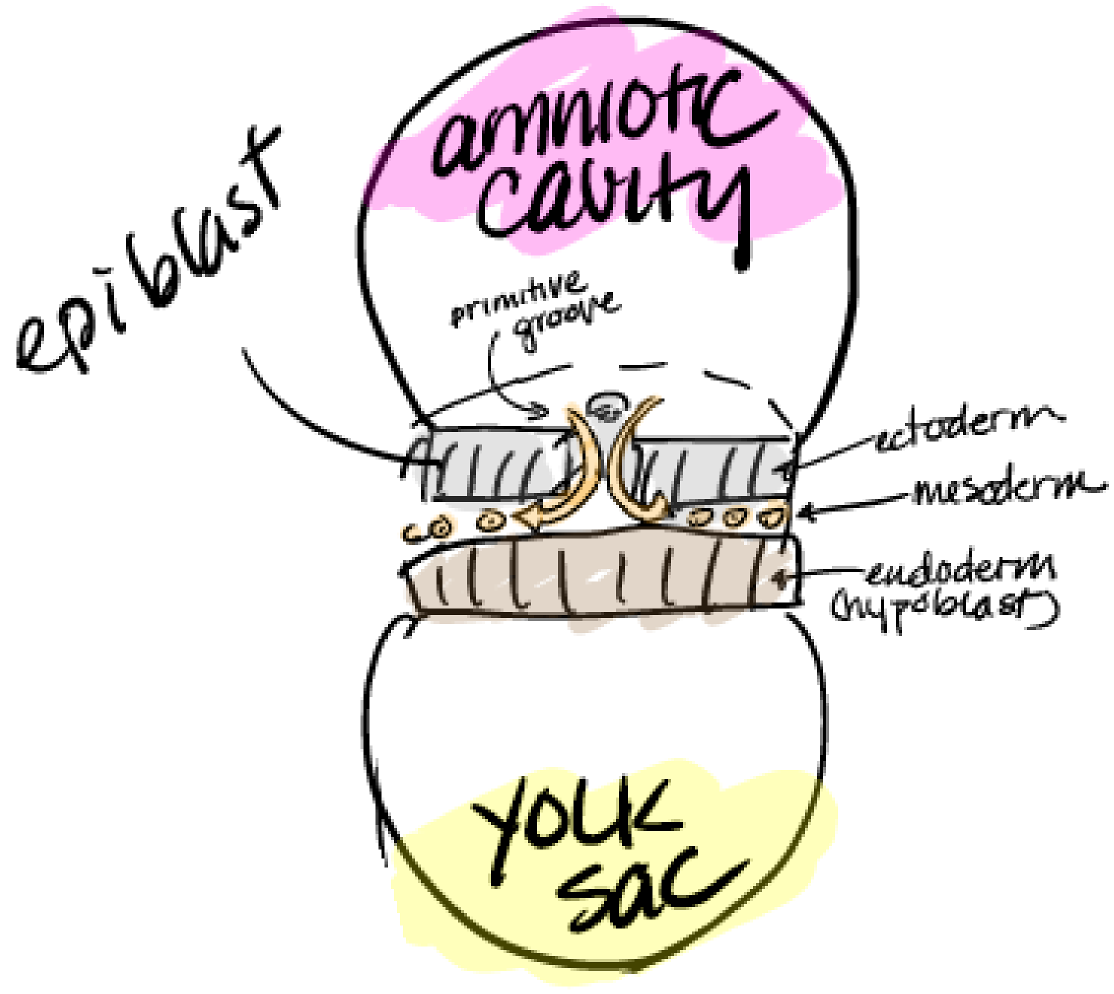


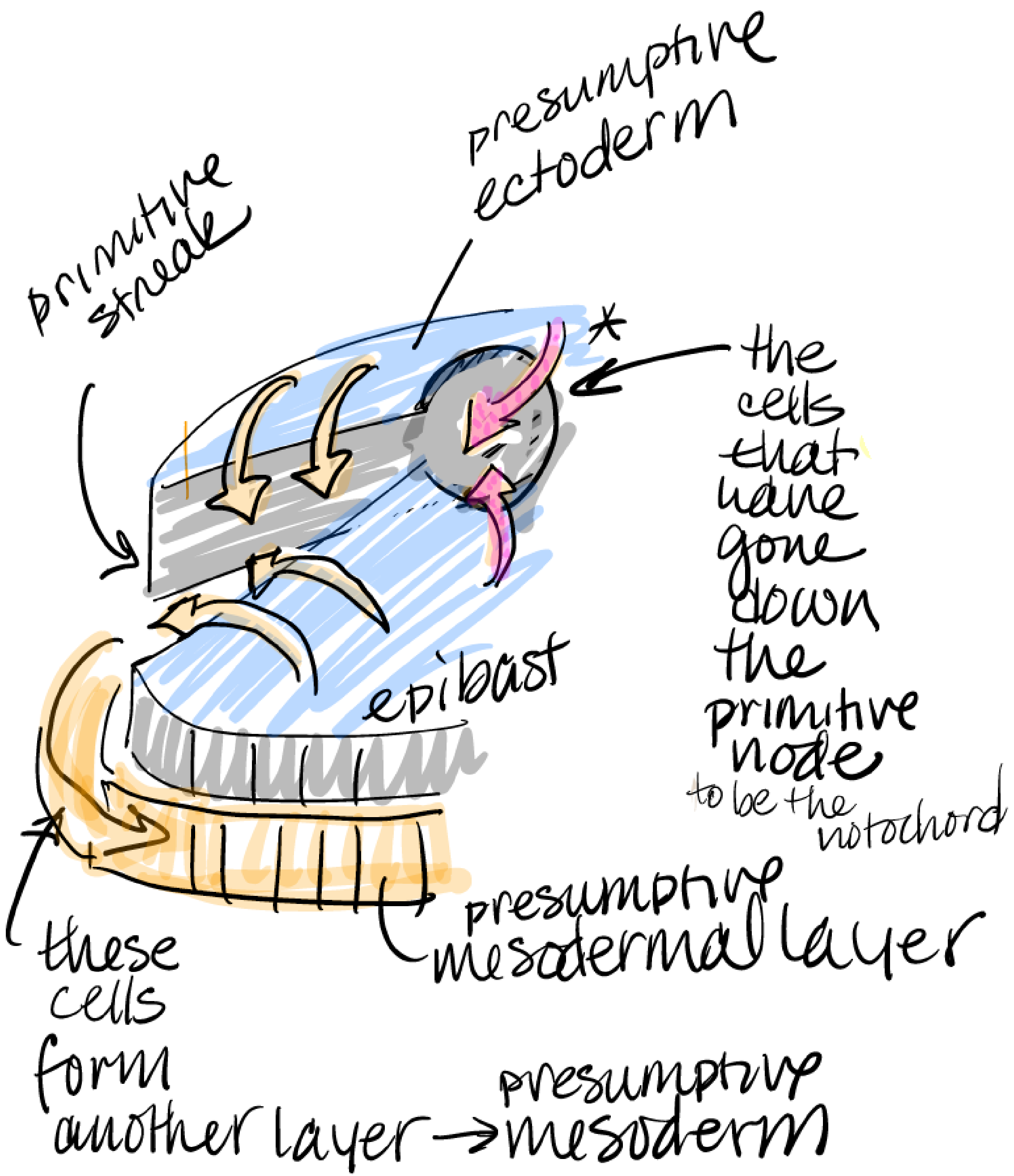

the cells on the side of the primitive streak start "slipping" & growing down into the primitive streak
epiblast

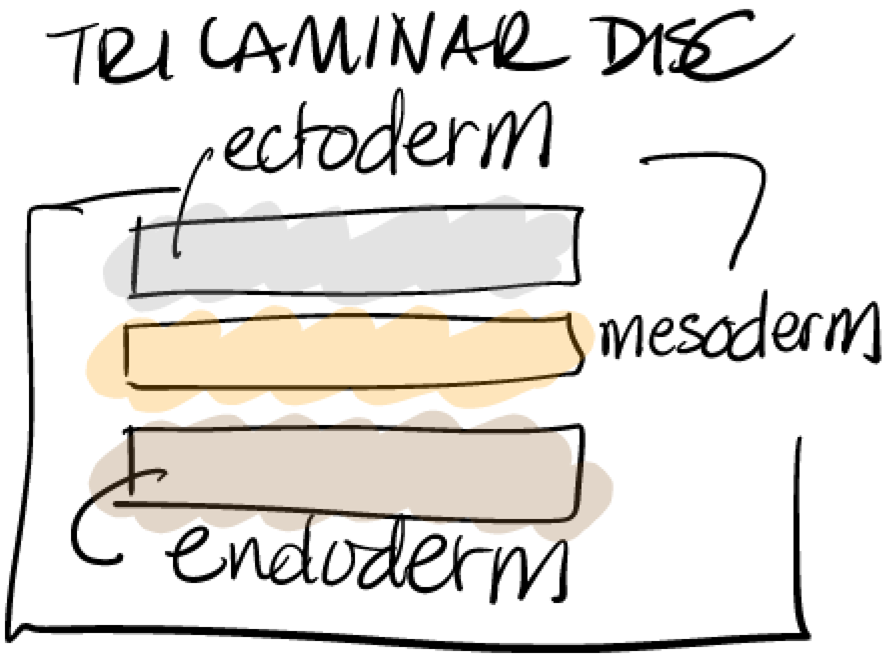


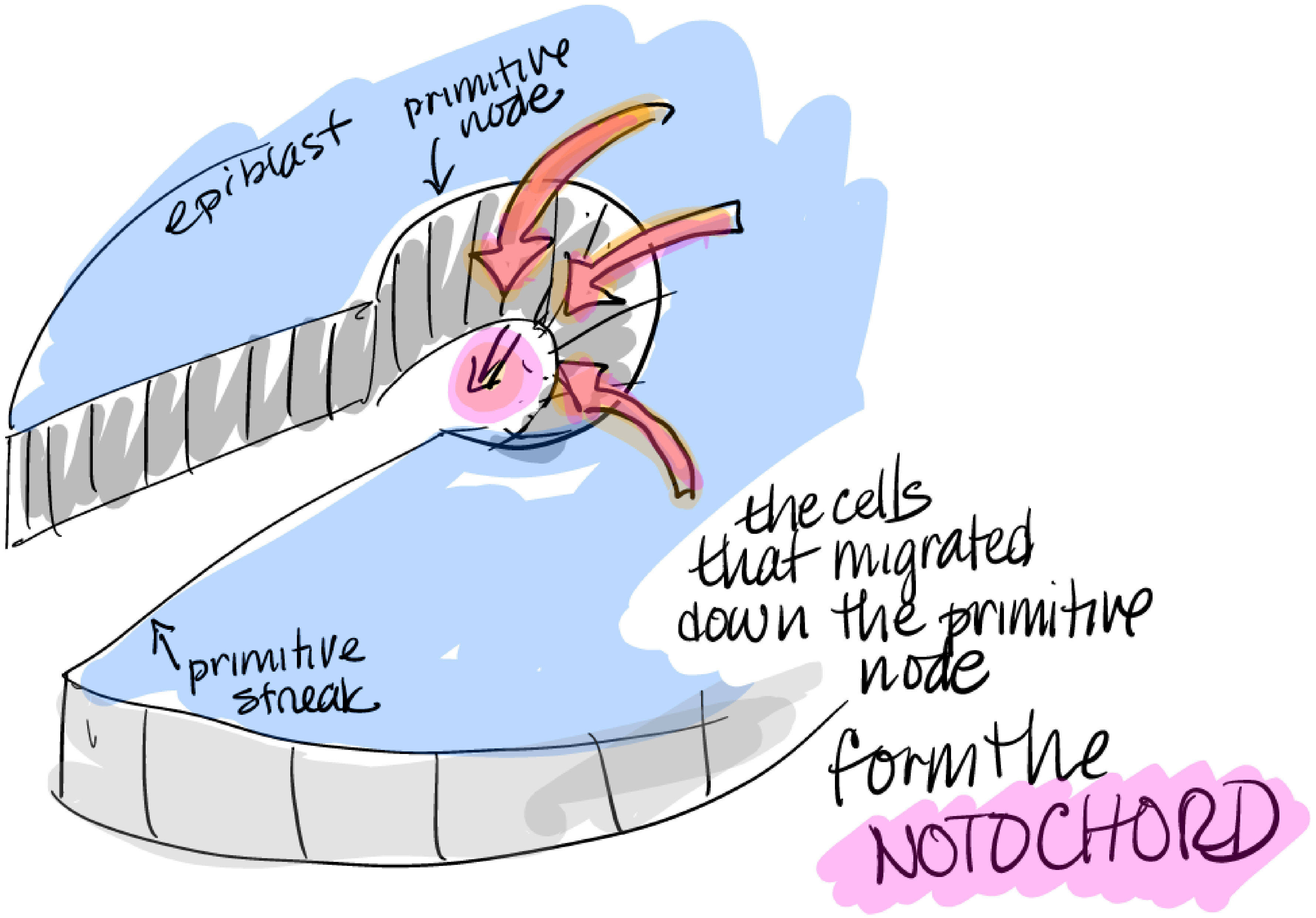
the cells are moving downward below the epiblast layer

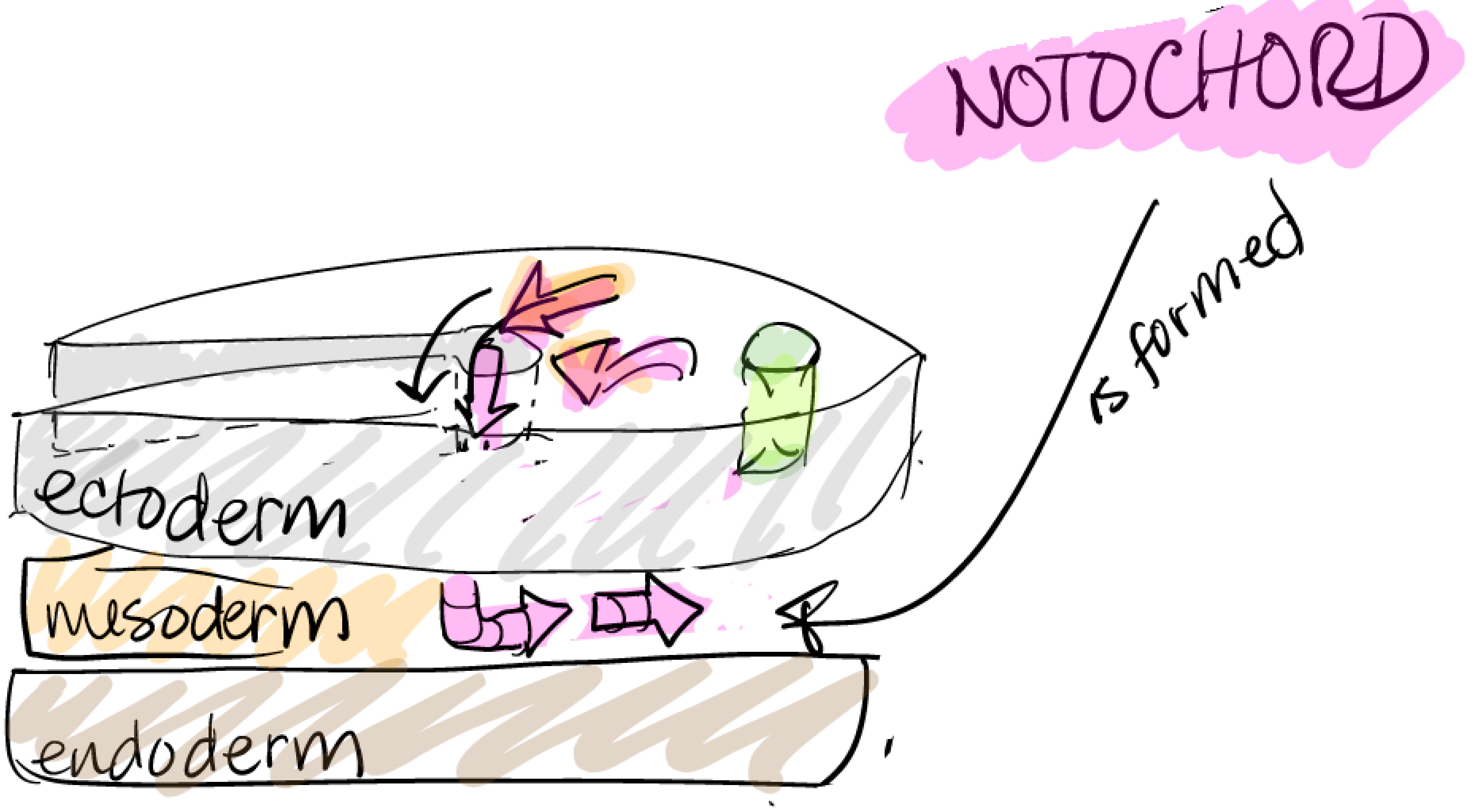

epibast


amniotic cavity
epiblast
primitive groove
ectoderm
mesoderm
endoderm (hypoblast)
yolk sac

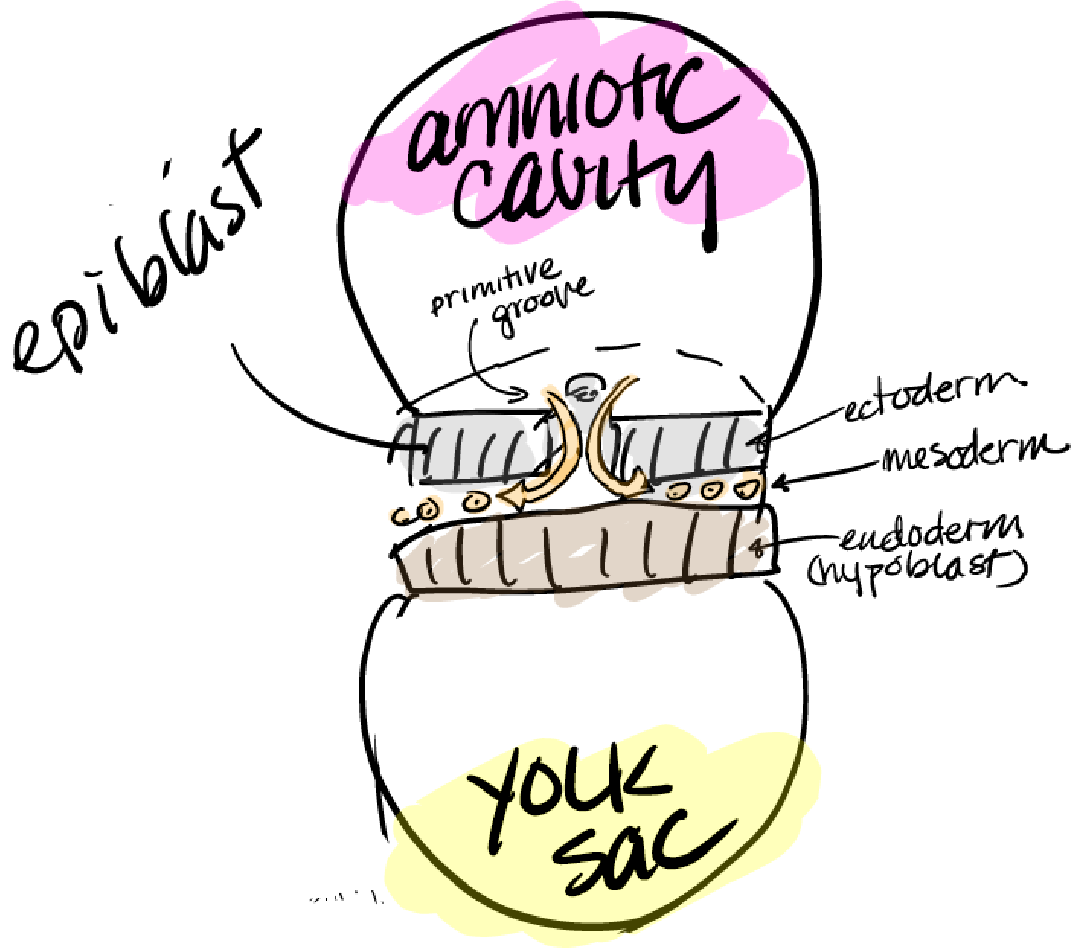

primitive streak
presumptive ectoderm
*
the cells that have gone down the primitive node
to be the notochord
epiblast
presumptive mesodermal layer
these cells form another layer → presumptive mesoderm

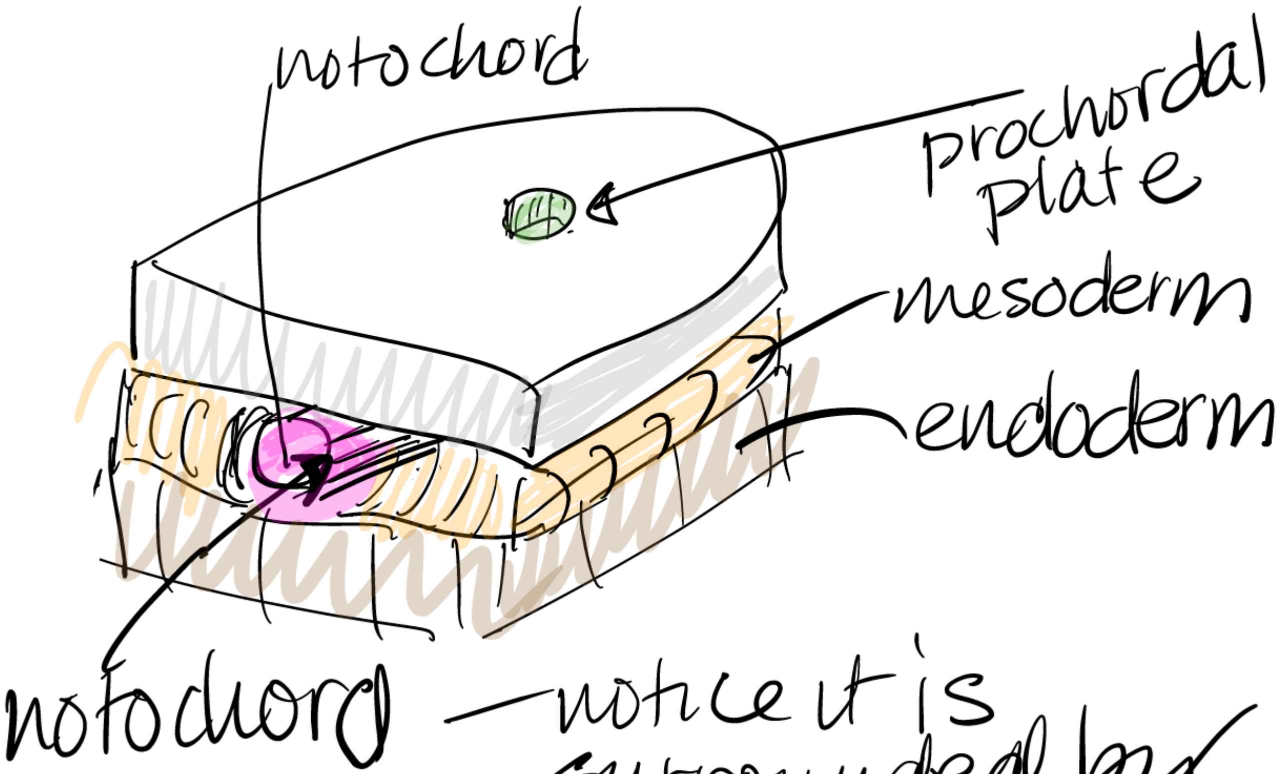

TRILAMINAR DISC
ectoderm
mesoderm
endoderm


epiblast
primitive node
primitive streak
the cells that migrated down the primitive node
form the NOTOCHORD


NOTOCHORD
is formed
ectoderm
mesoderm
endoderm

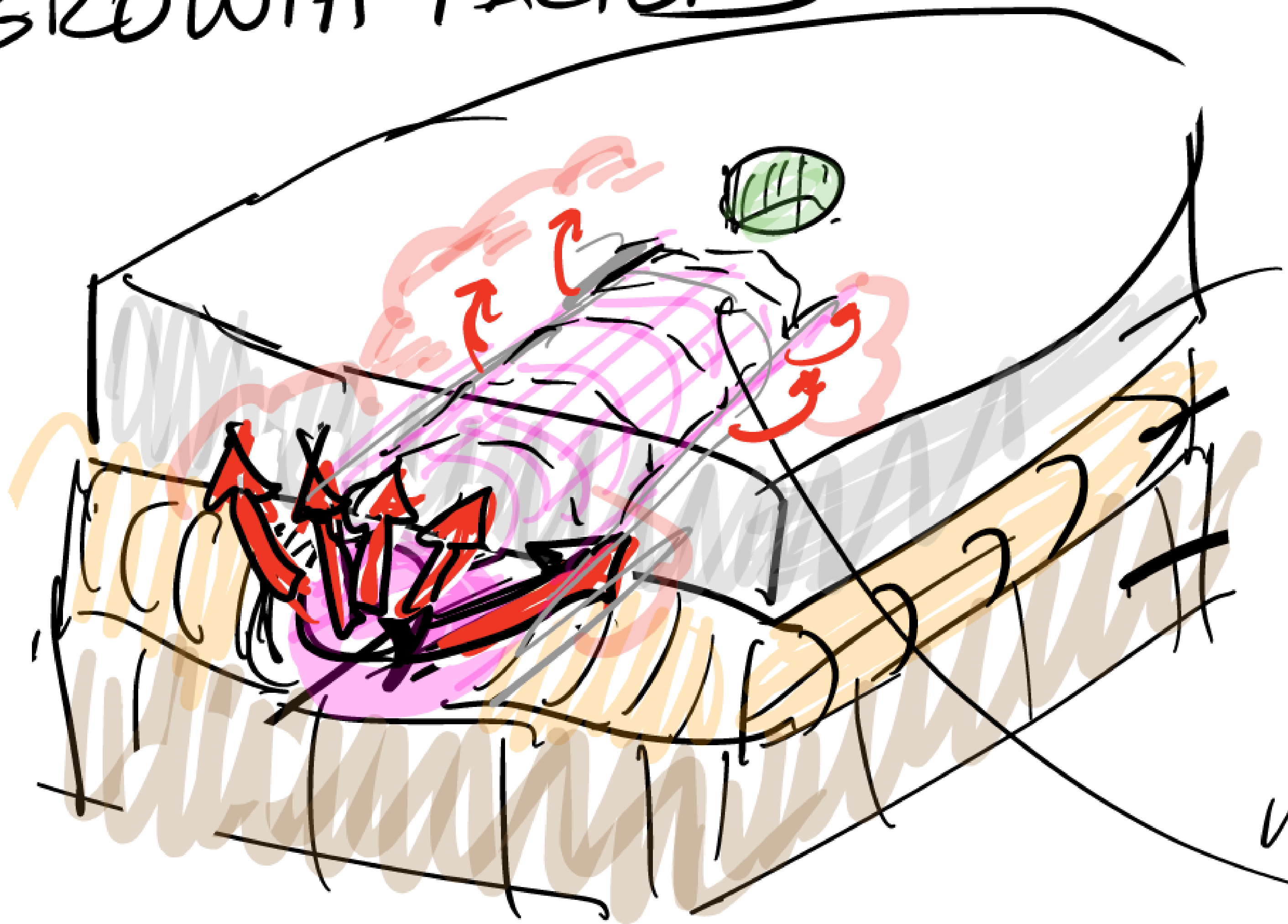
3RD Week

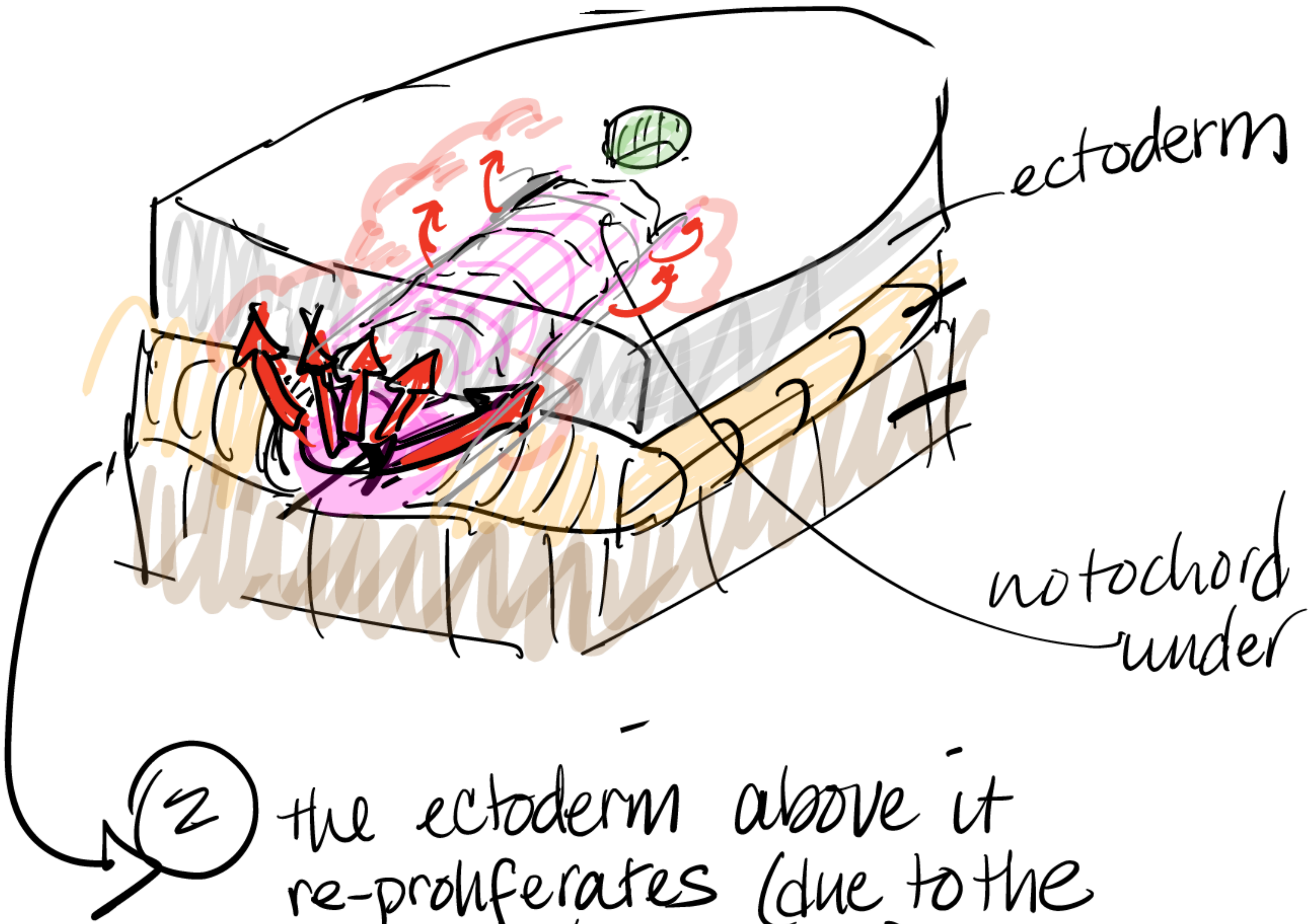

amniotic cavity
epiblast
primitive groove
ectoderm
mesoderm
endoderm (hypoblast)
yolk sac



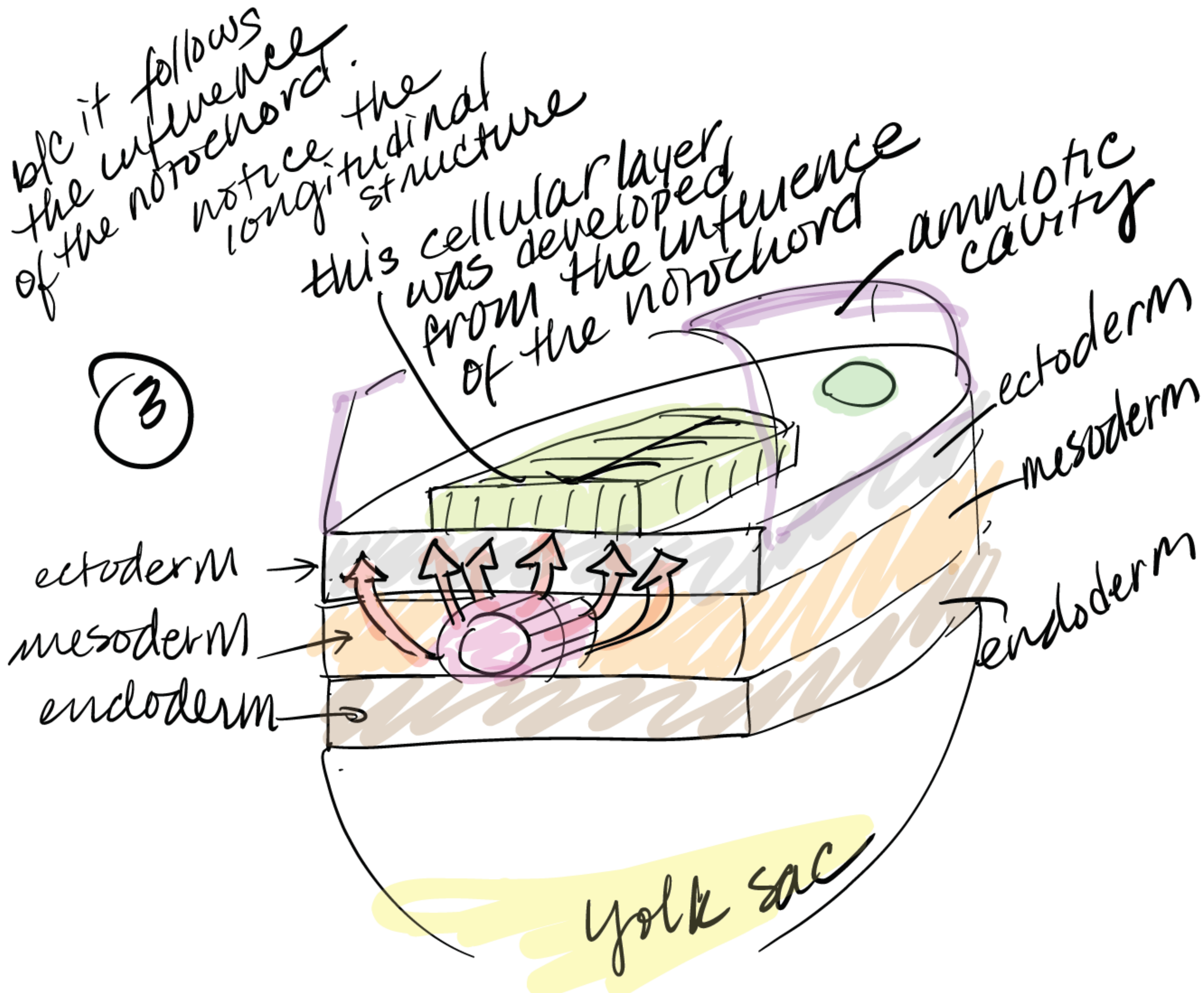
– notice it is surrounded by mesoderm on the sides
→ ectoderm & endoderm above & below

① NOTOCHORD RELEASES GROWTH FACTORS

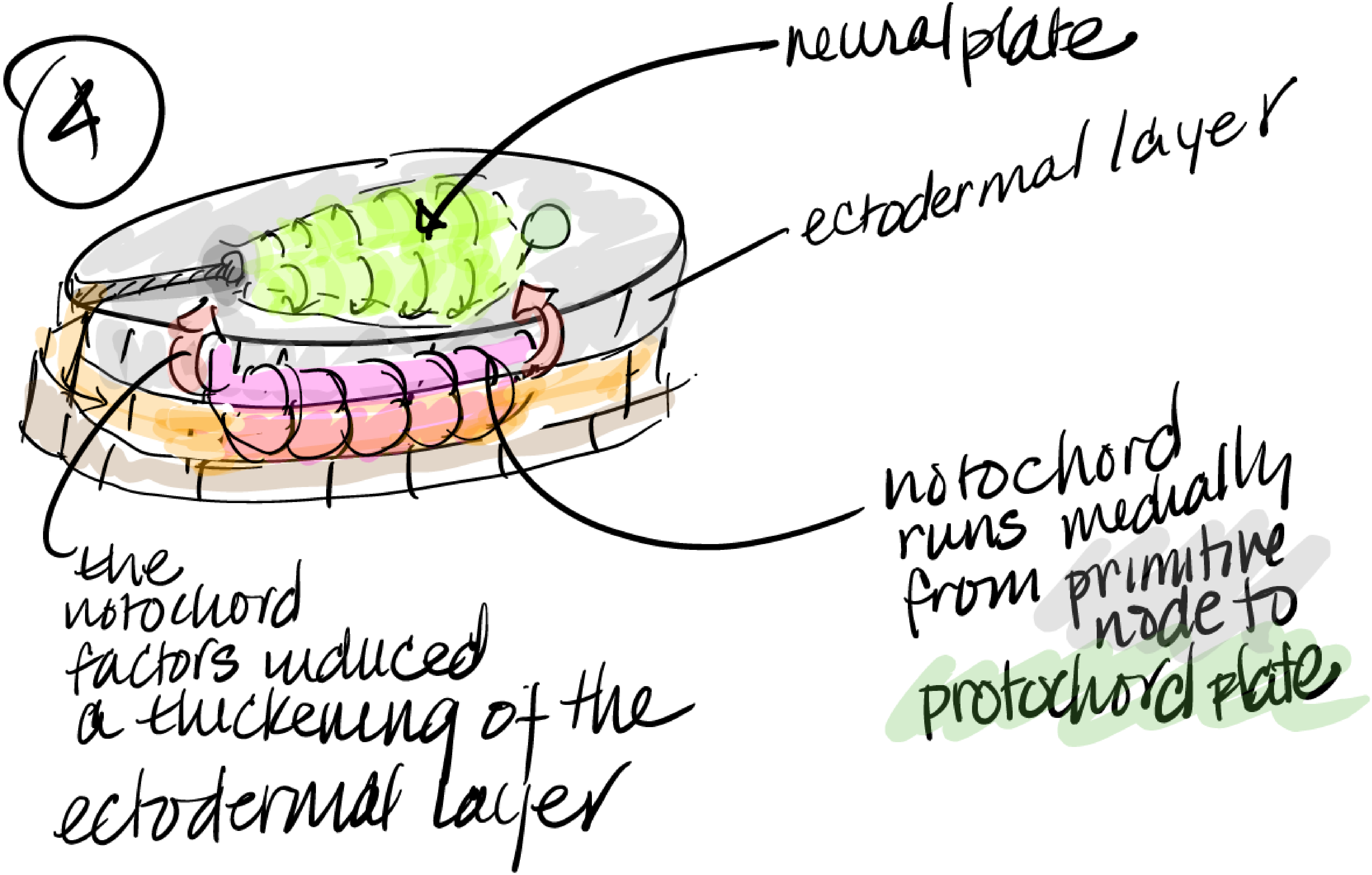




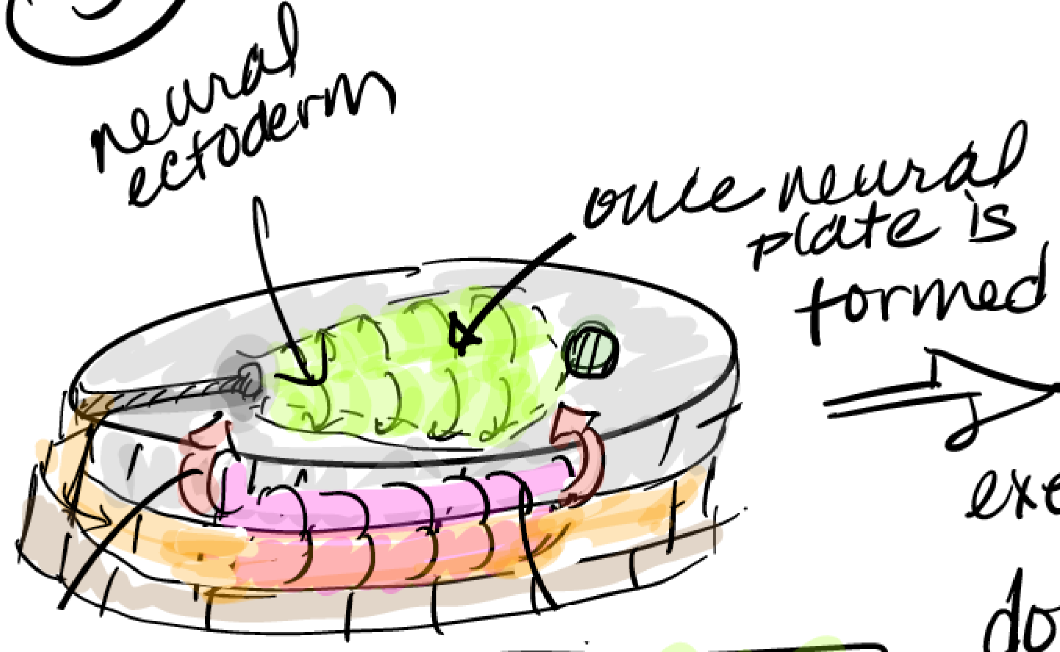
(2) the ectoderm above it re-proliferates (due to the notochord signals)
→ the ectoderm will start to develop thickening



b/c it follows the influence of the notochord.
notice the longitudinal structure
this cellular layer was developed from the influence of the notochord
amniotic cavity
3
ectoderm
mesoderm
endoderm
ectoderm
mesoderm
endoderm
Yolk sac


4
neural plate
ectodermal layer
notochord runs medially from primitive node to protochord plate
the notochord factors induced a thickening of the ectodermal layer

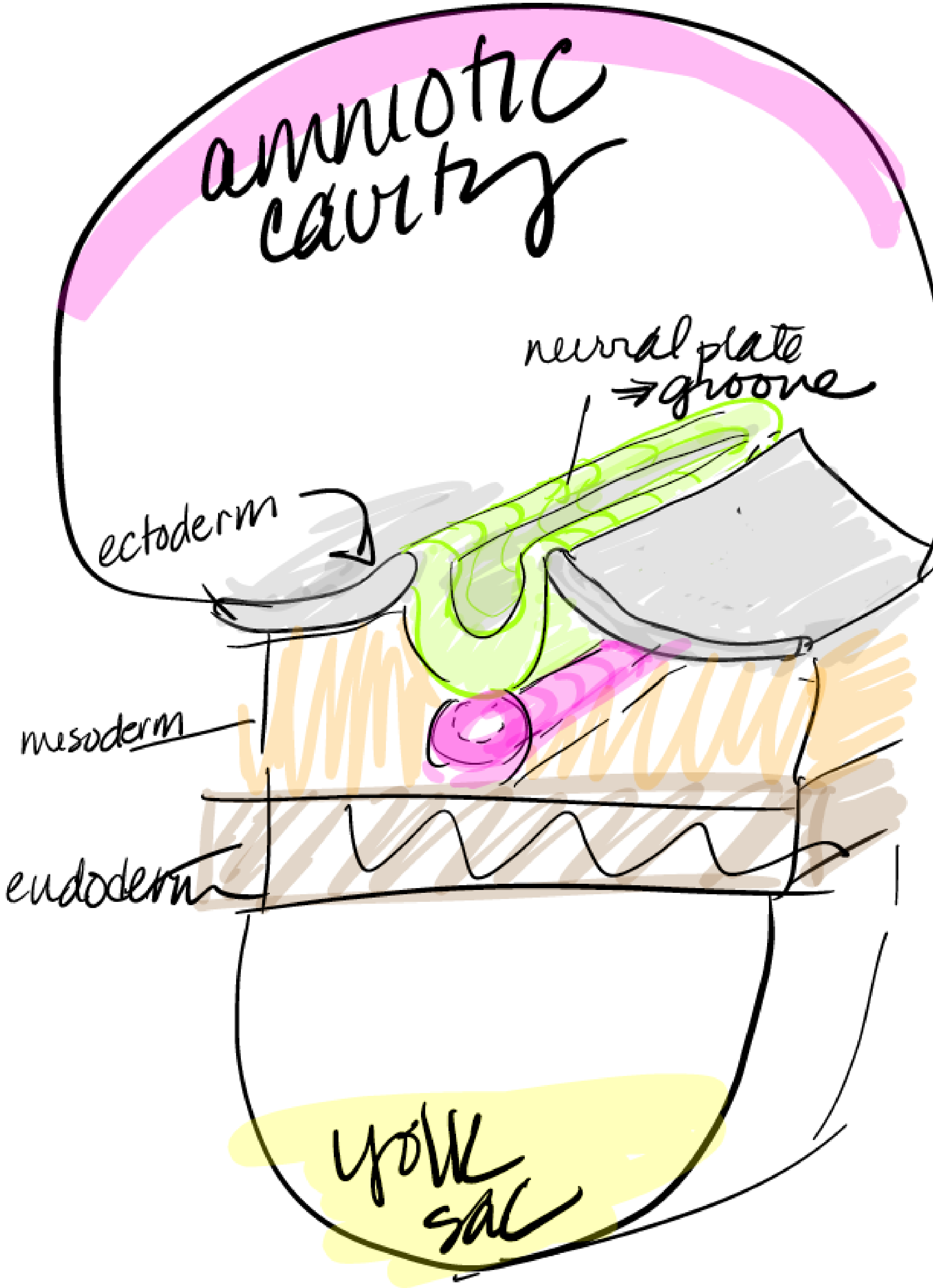
5



neurulation

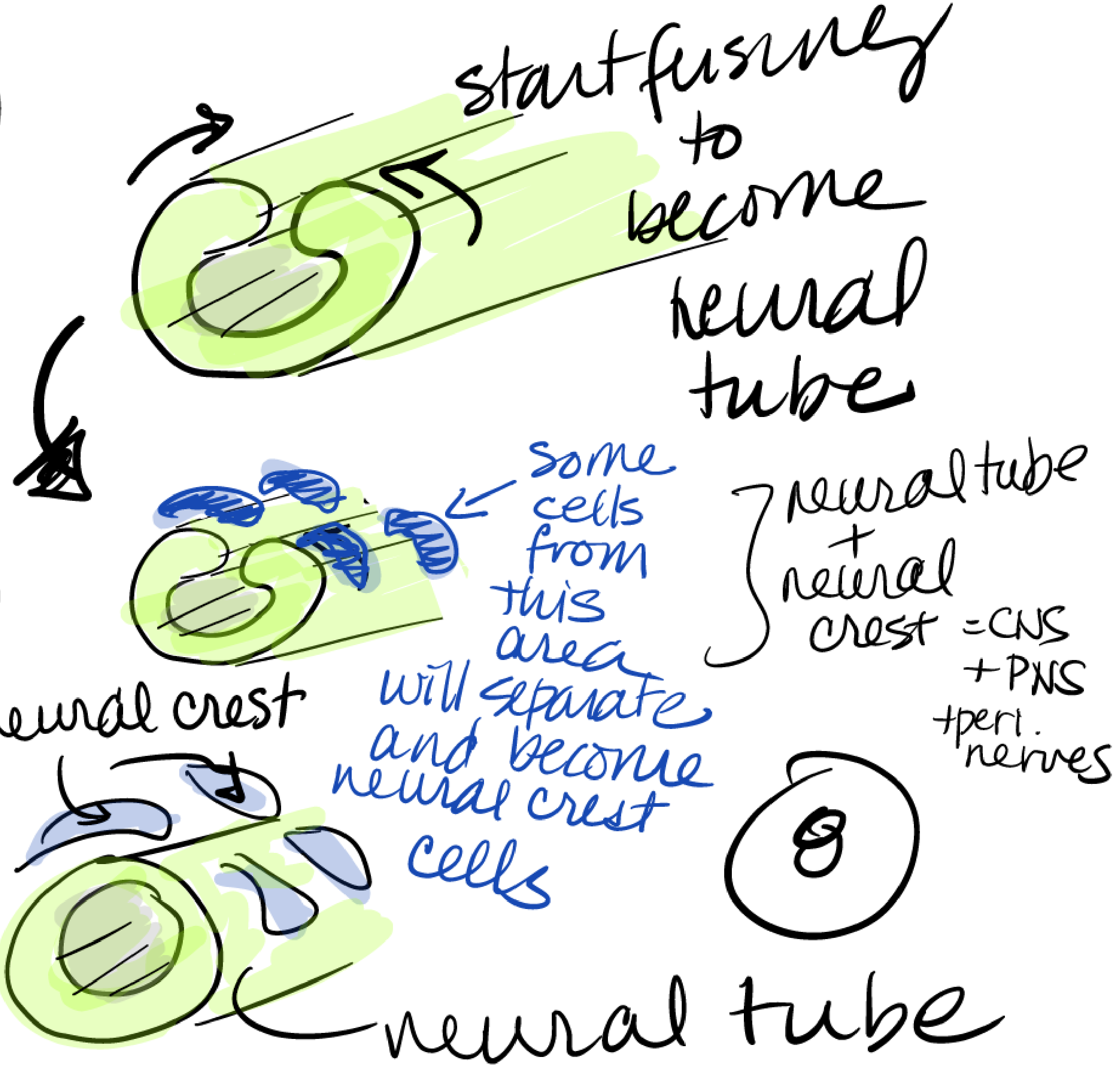
⟹ it will exert ⇓ downward pressure as it folds as the edges rise and the center depresses

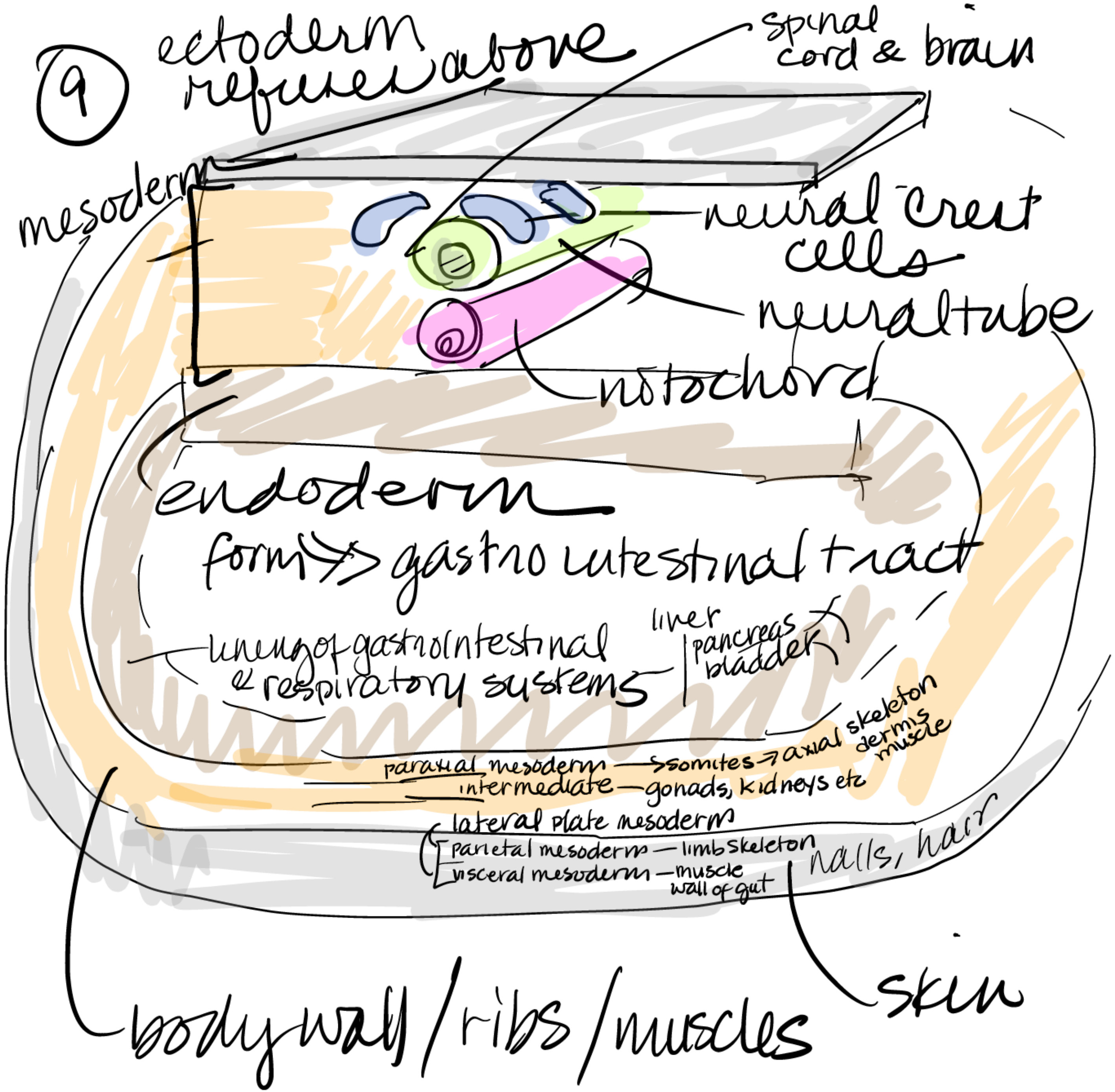
6


amniotic cavity
neural plate
groove
ectoderm
mesoderm
endoderm
yolk sac

7

the neural crest cells separate as neural groove closes into a tube

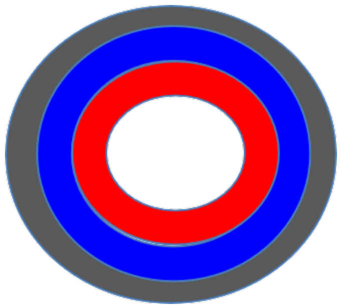




9
ectoderm refer above
spinal cord & brain
mesoderm
neural crest cells
neuraltube
notochord
endoderm
form gastro intestinal tract
lining of gastrointestinal & respiratory systems
liver
pancreas
bladder
paraxial mesoderm — somites → axial skeleton dermis muscle
intermediate — gonads, kidneys etc
lateral plate mesoderm
parietal mesoderm — limb skeleton
visceral mesoderm — muscle wall of gut
nails, hair
skin
body wall / ribs / muscles

Embryonic Development

Initially, the embryo has 3 distinct layers of cells



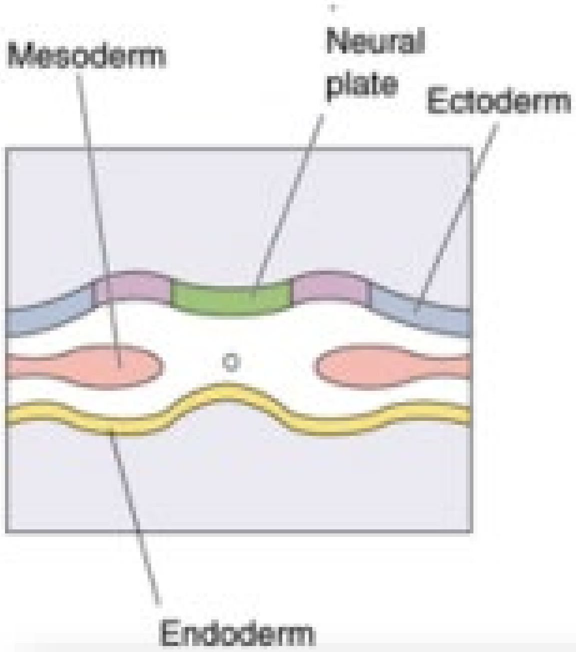
Ectoderm >> Nervous System & Skin **Mesoderm**

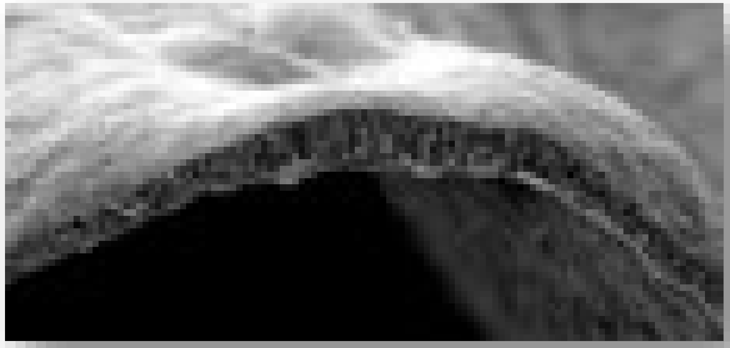
>> Muscles, Bone **Endoderm**

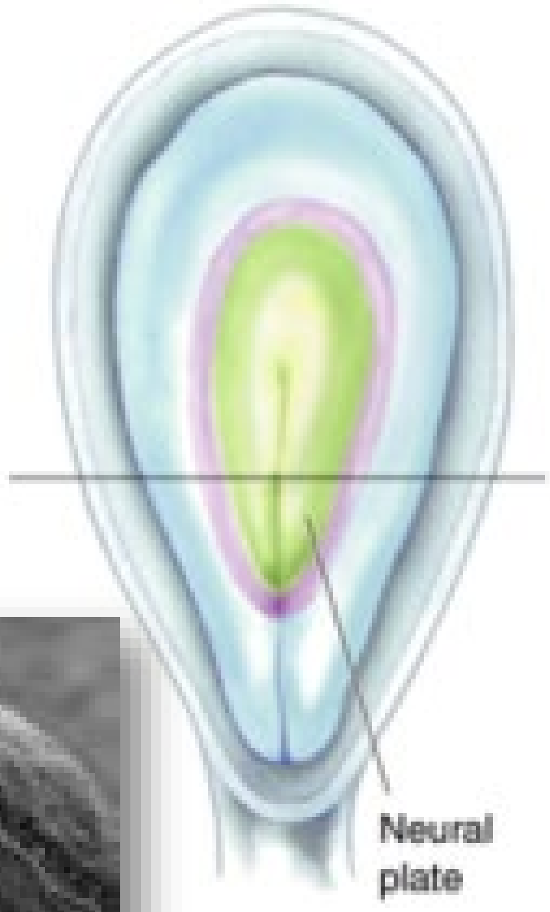
>> Organs

E7-3 layered flat disk

- **endoderm** → Lining of internal organs (viscera)
- **mesoderm** → Muscles and skeletal bones
- **ectoderm** → Skin and nervous system

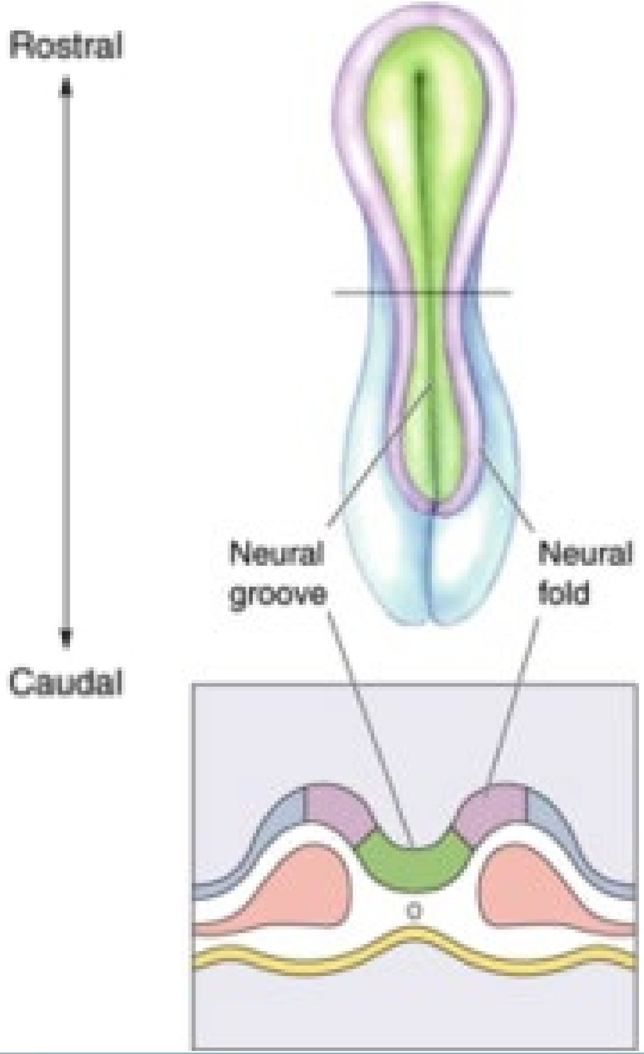




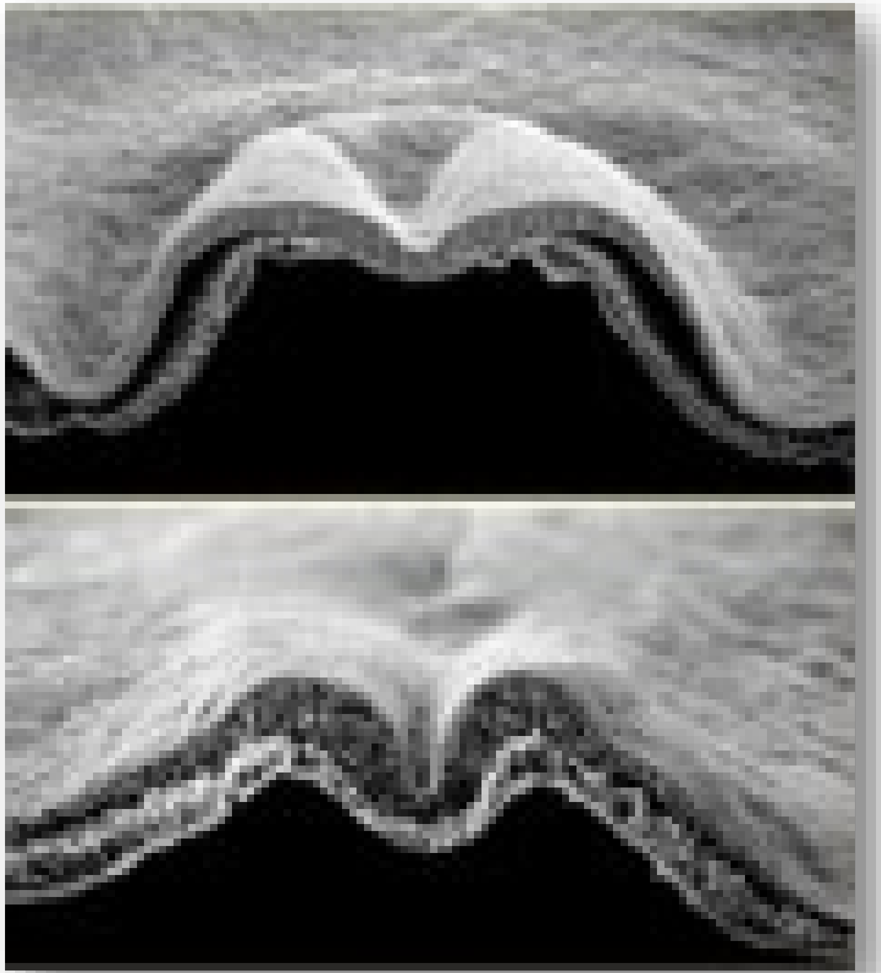


(See pages 180-184 in Bear et al text)

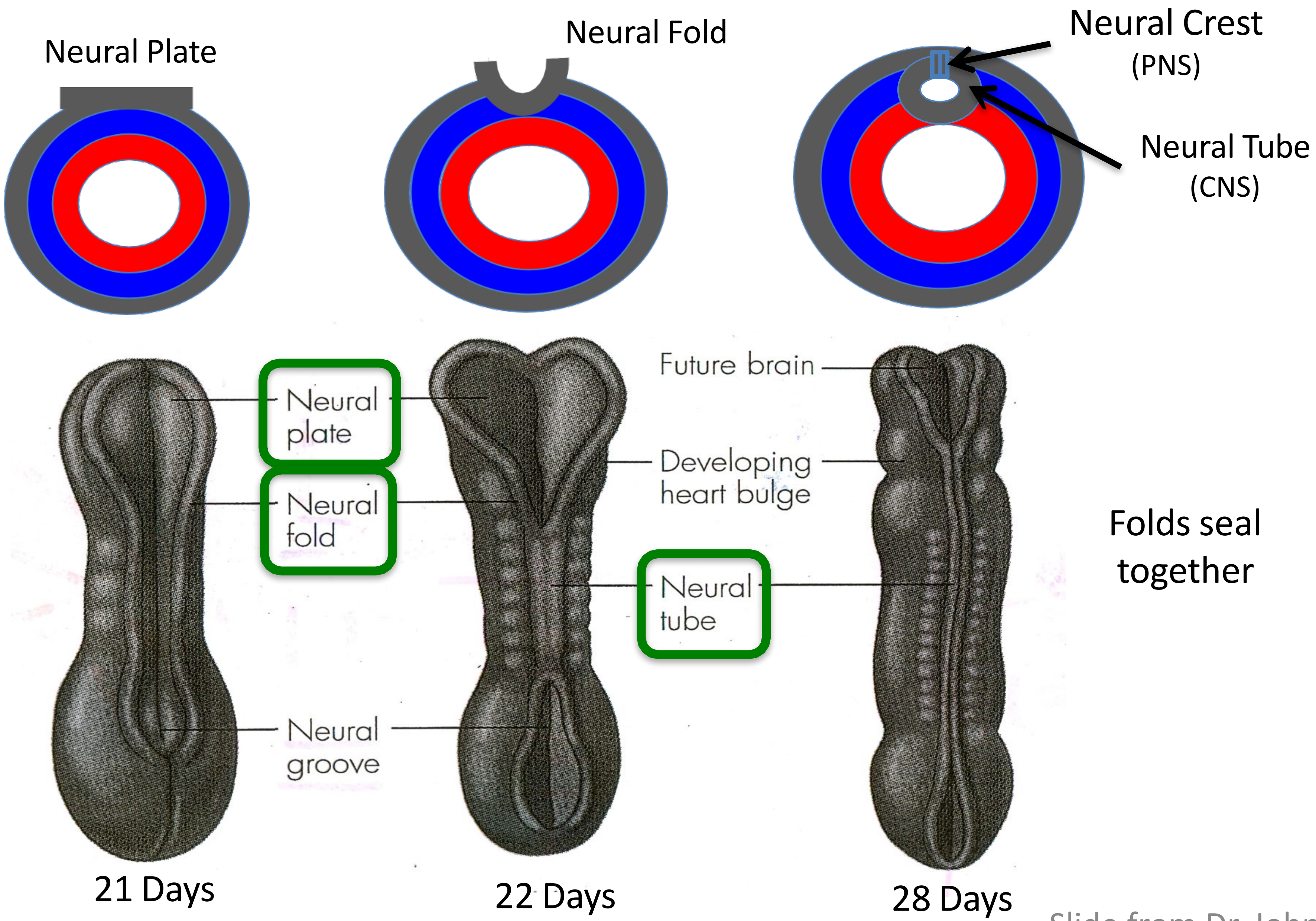
Formation of neural groove



The neural folds eventually come together and fuse becoming the neural tube.

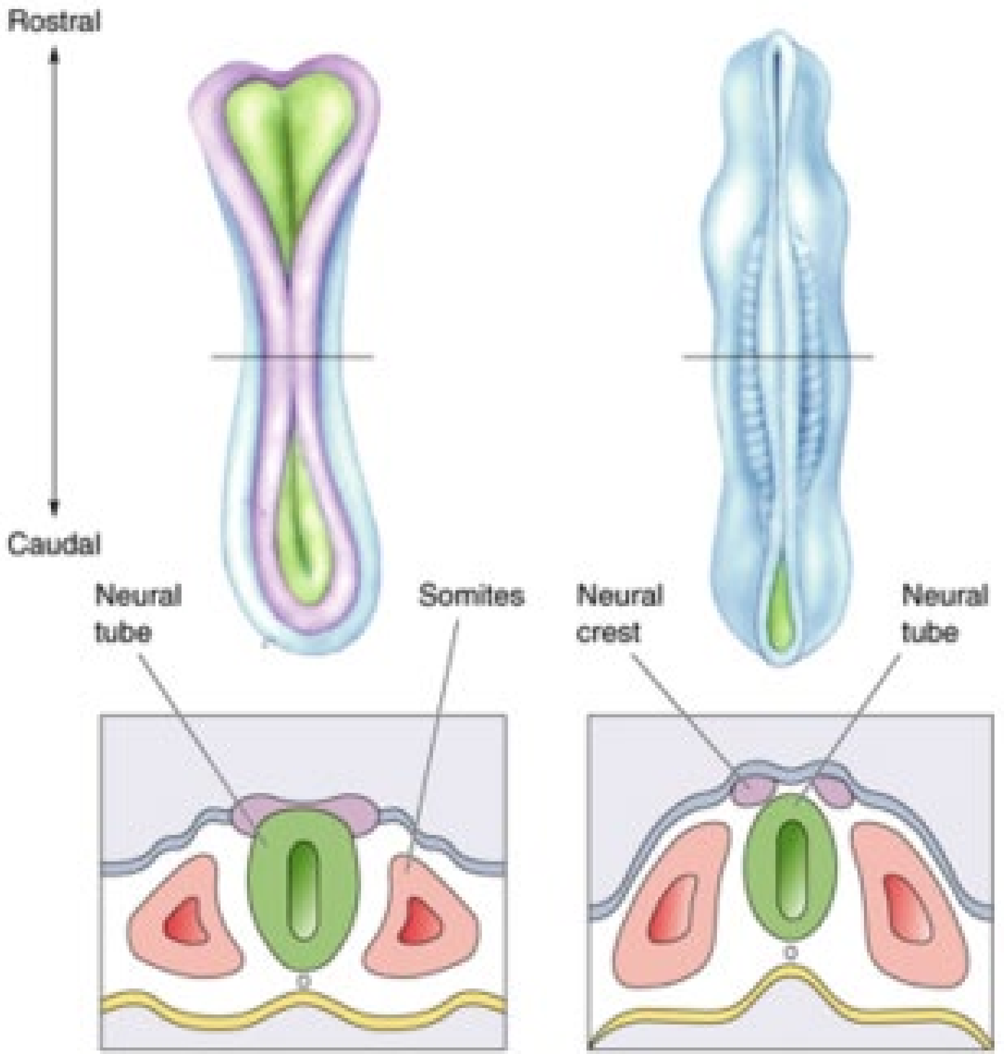


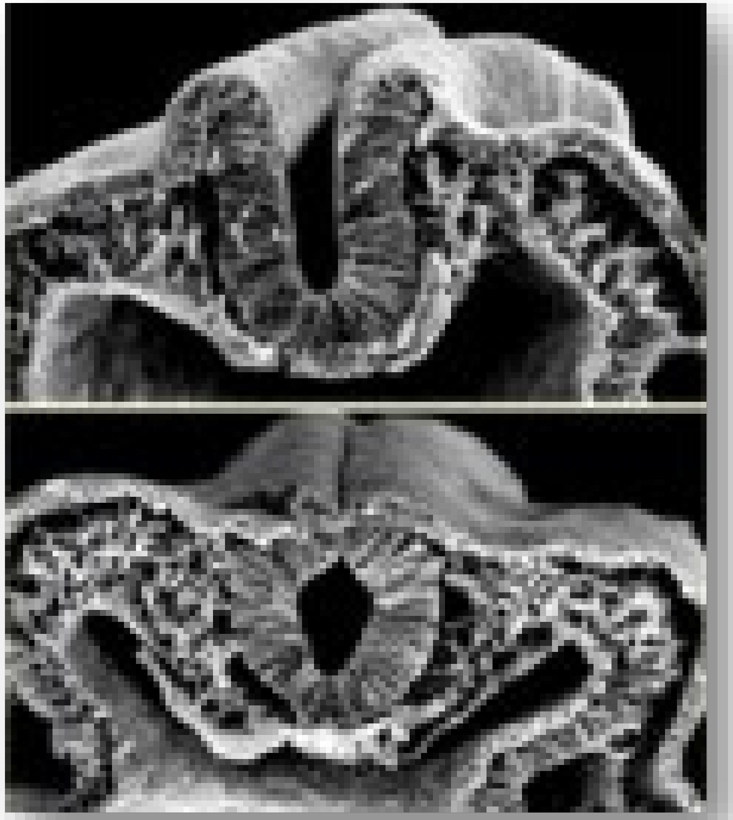
Embryonic Development



Folds seal together

E22: Neurulation→ Becoming a neural tube

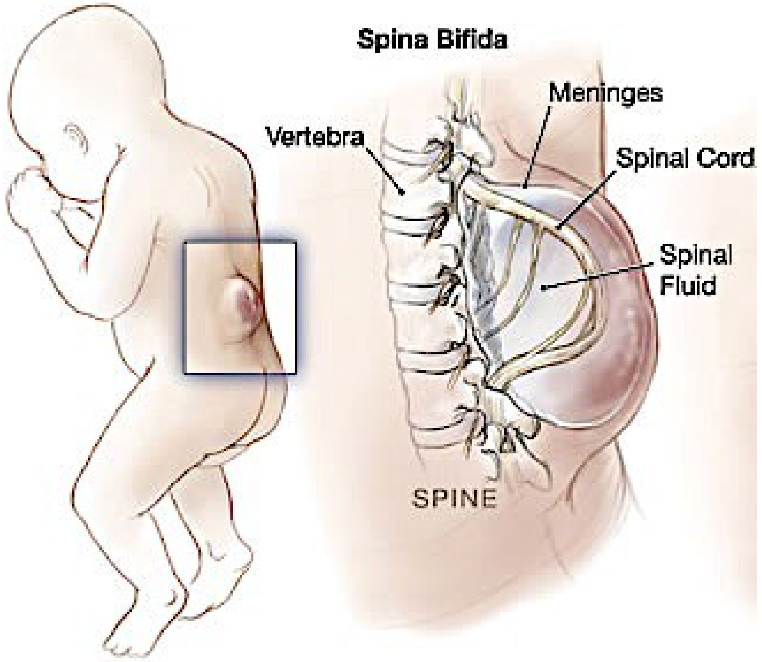




Somites → muscle and bones
Neural crest → PNS

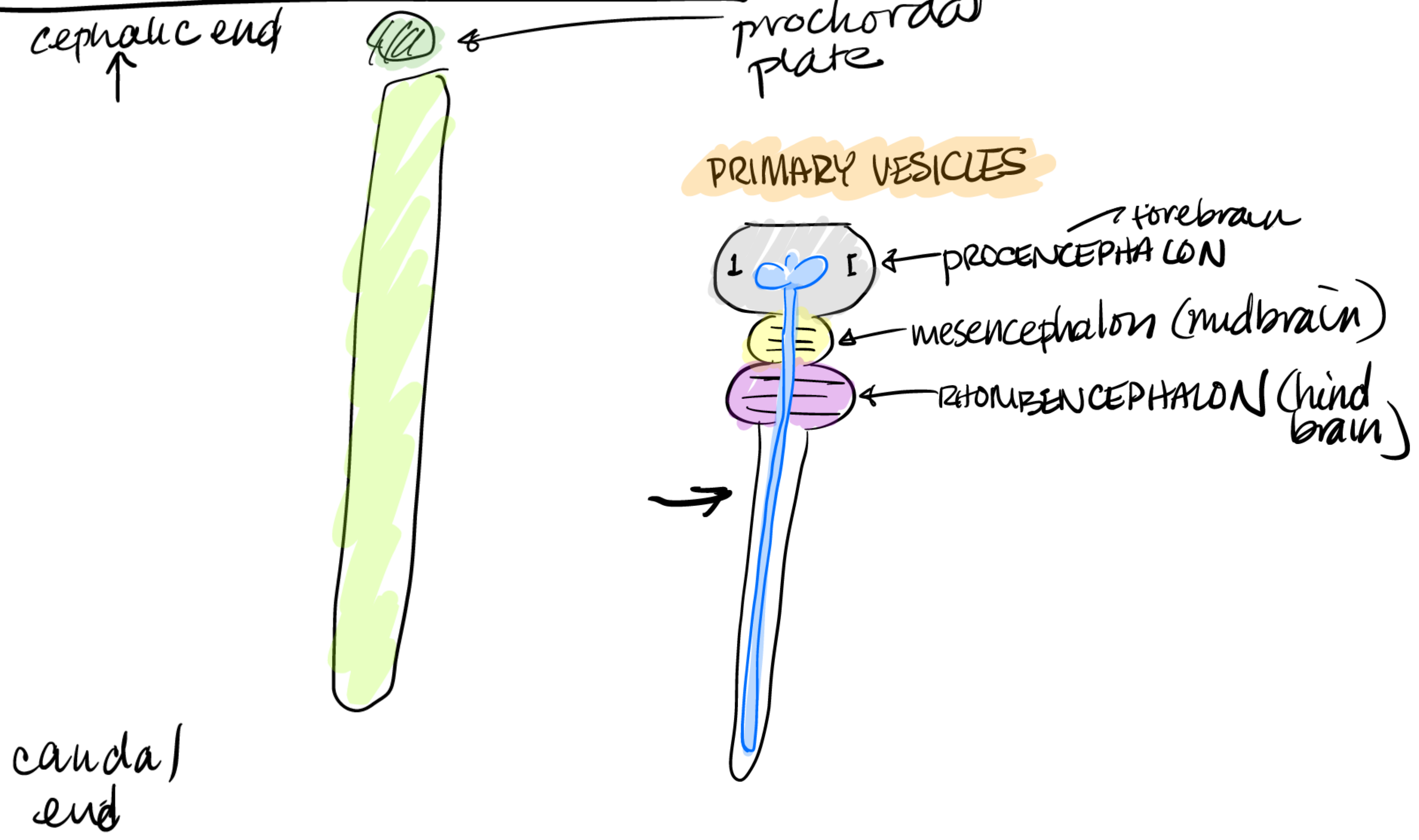
Spina Bifida

Neural Folds fail to join



Slide from Dr. Johnson's COGS17

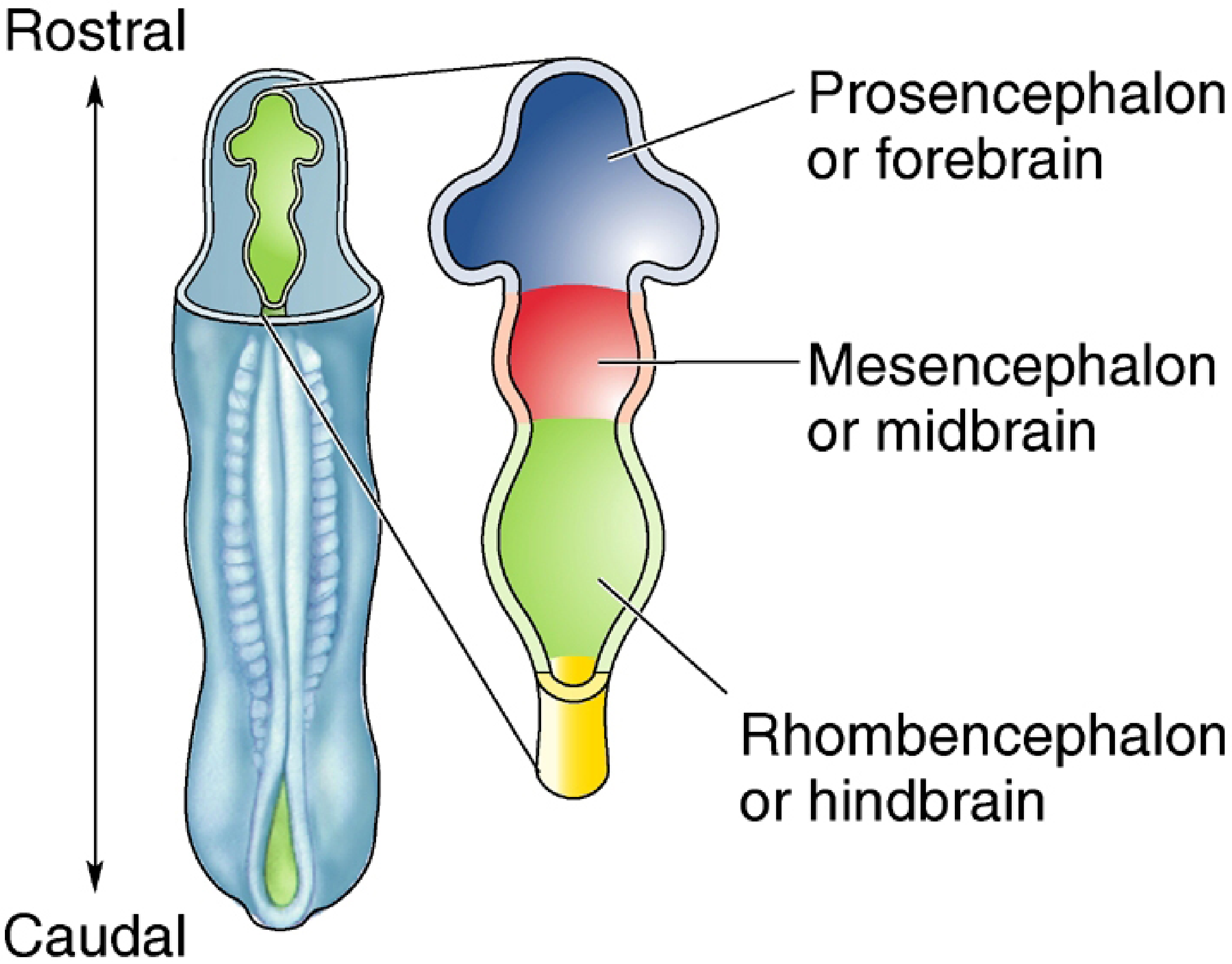
Derivatives of Neural Tube



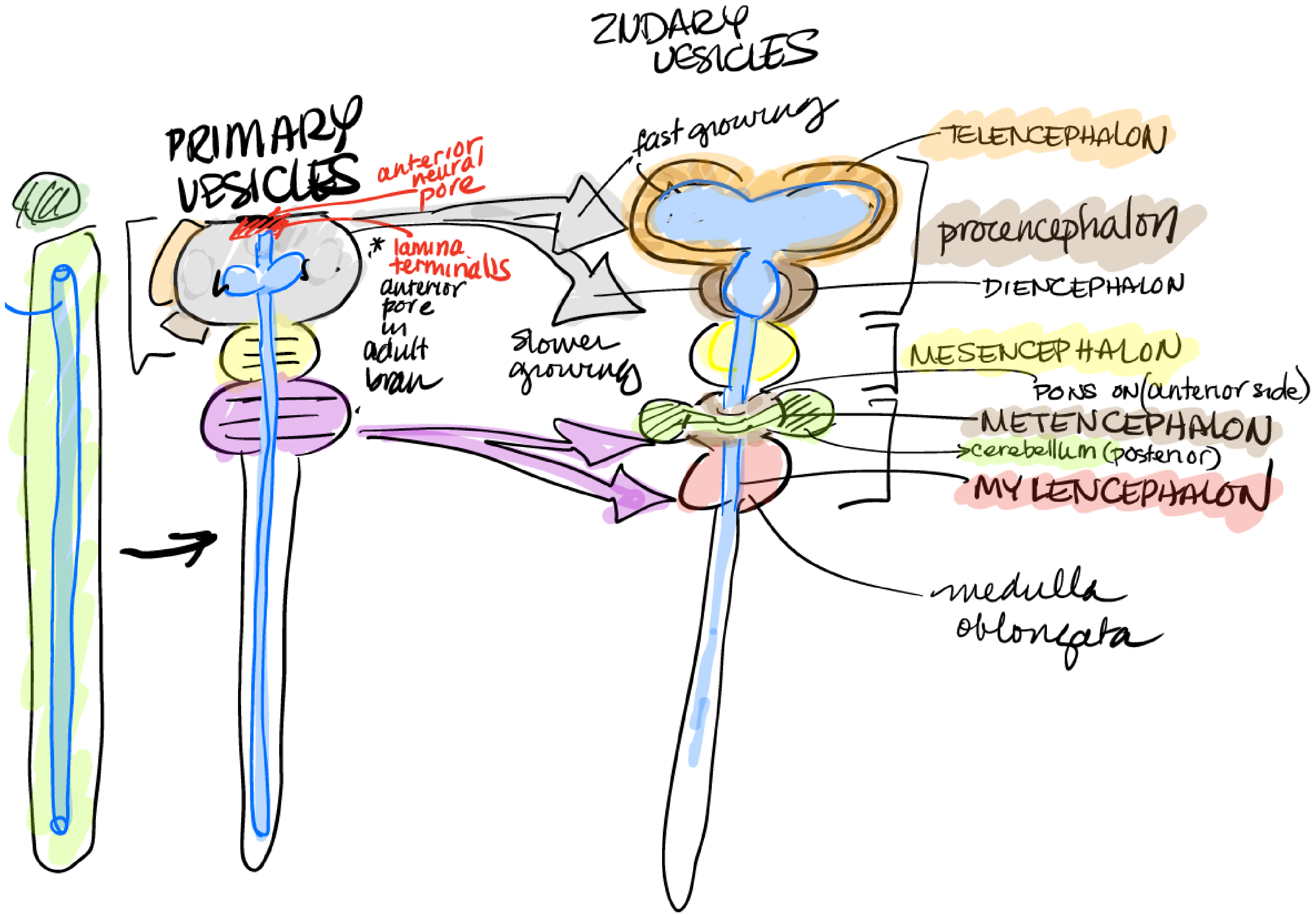
In the beginning…(Three primary vesicles)

The rostral end of the neural tube **differentiates** to form the three vesicles that will give rise to the entire brain.

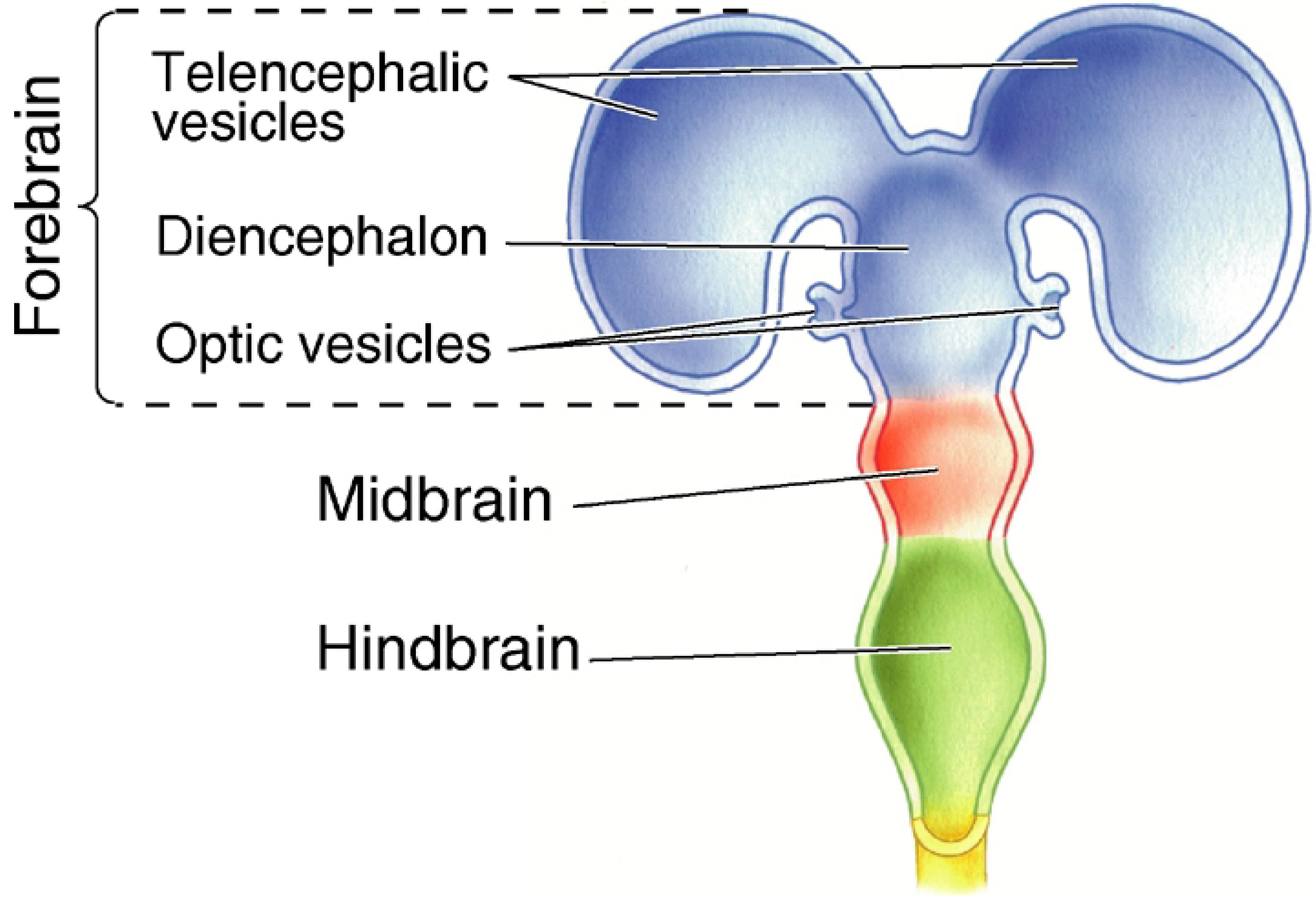
In this figure one can see inside the neural tube.



Differentiation: the process by which structures become more complex and functionally specialized during development.


PRIMARY VESICLES
anterior neural pore
* lamina terminalis
anterior pore in adult brain
2NDARY VESICLES
fast growing
slower growing
TELENCEPHALON
procencephalon
DIENCEPHALON
MESENCEPHALON
PONS ON (anterior side)
METENCEPHALON
cerebellum (posterior)
MYLENCEPHALON
medulla oblongata

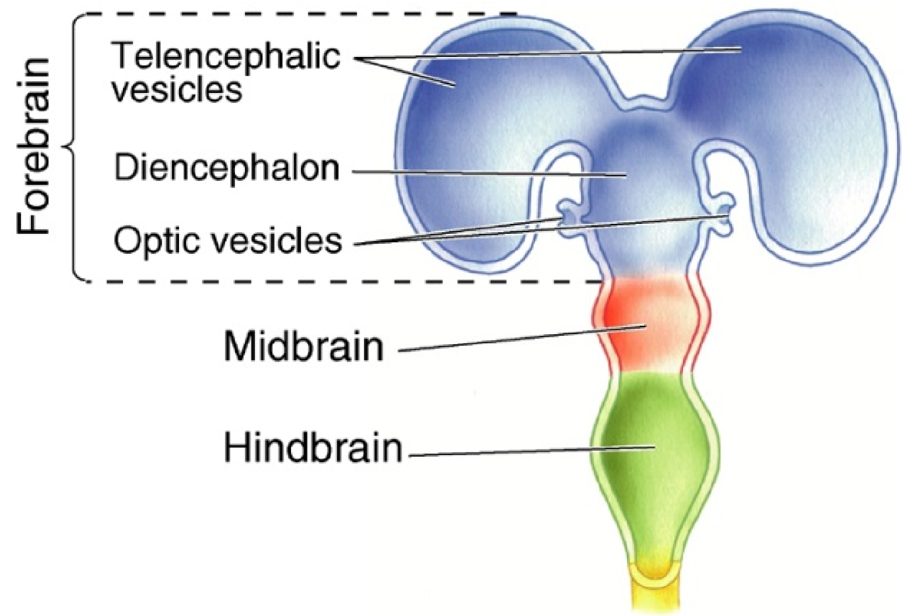
Secondary vesicles...



The **secondary** brain vesicles of the forebrain:

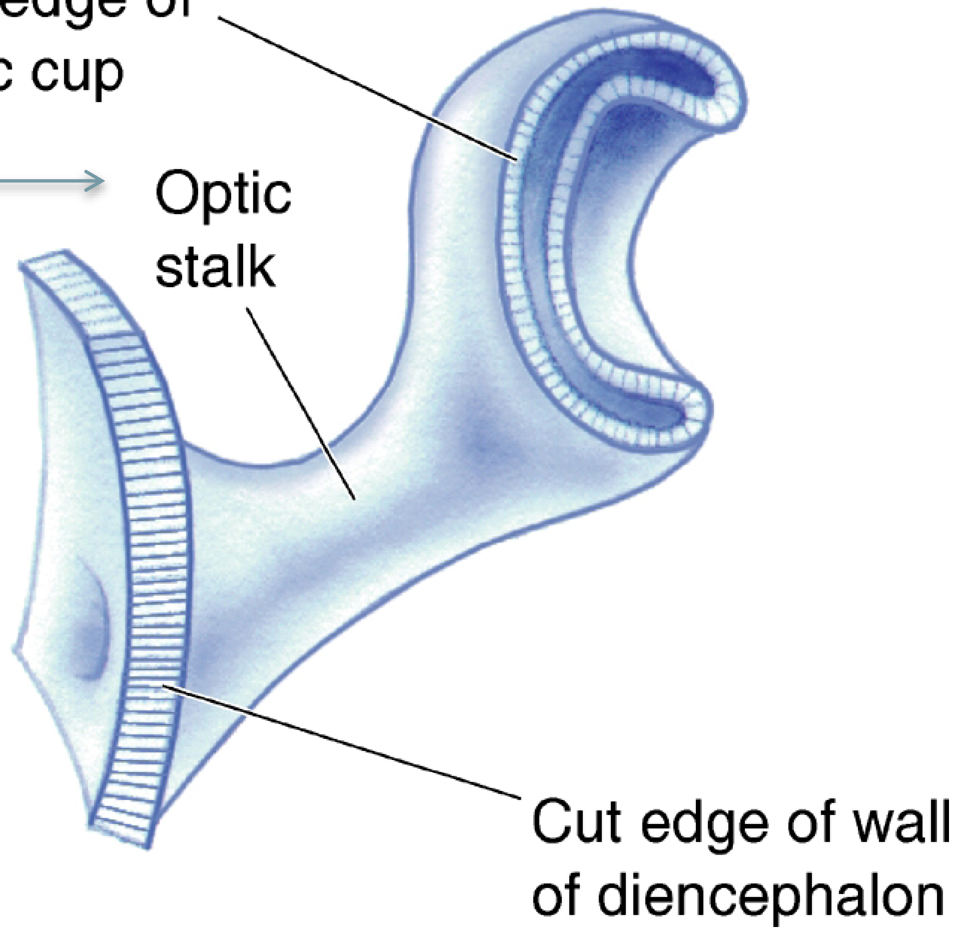
The forebrain differentiates into the paired **telencephalic** and **optic** vesicles.

Early development of the eye...

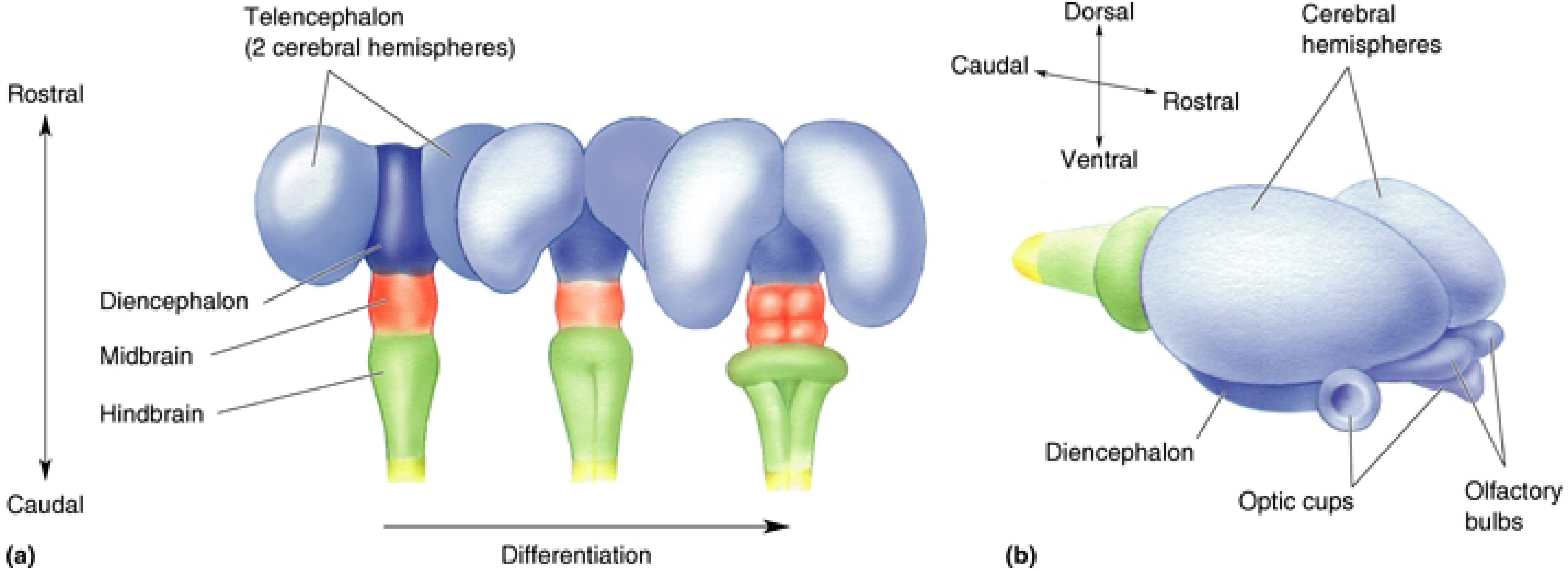


will become retina → Cut edge of optic cup

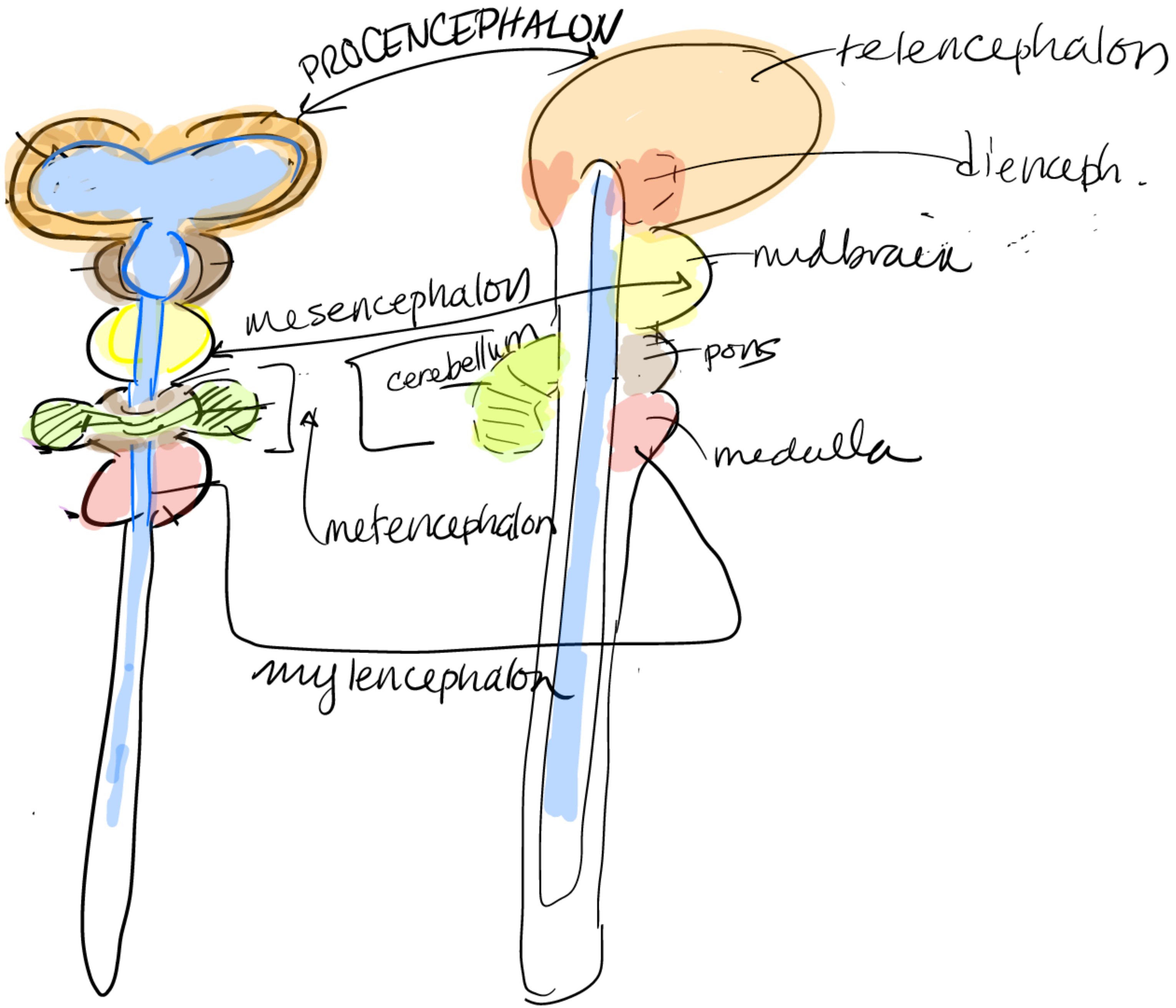
will become optic nerve → Optic stalk

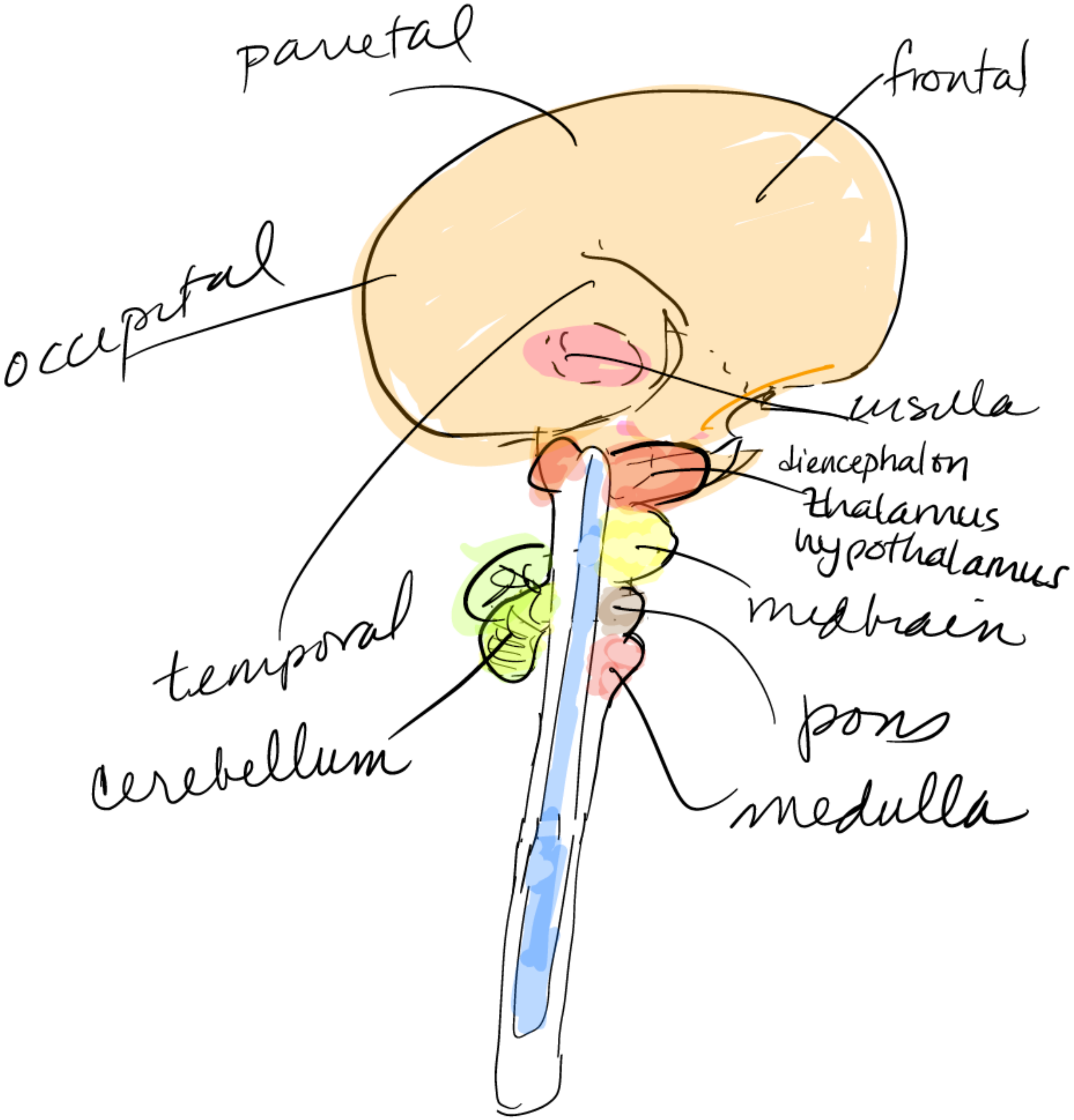


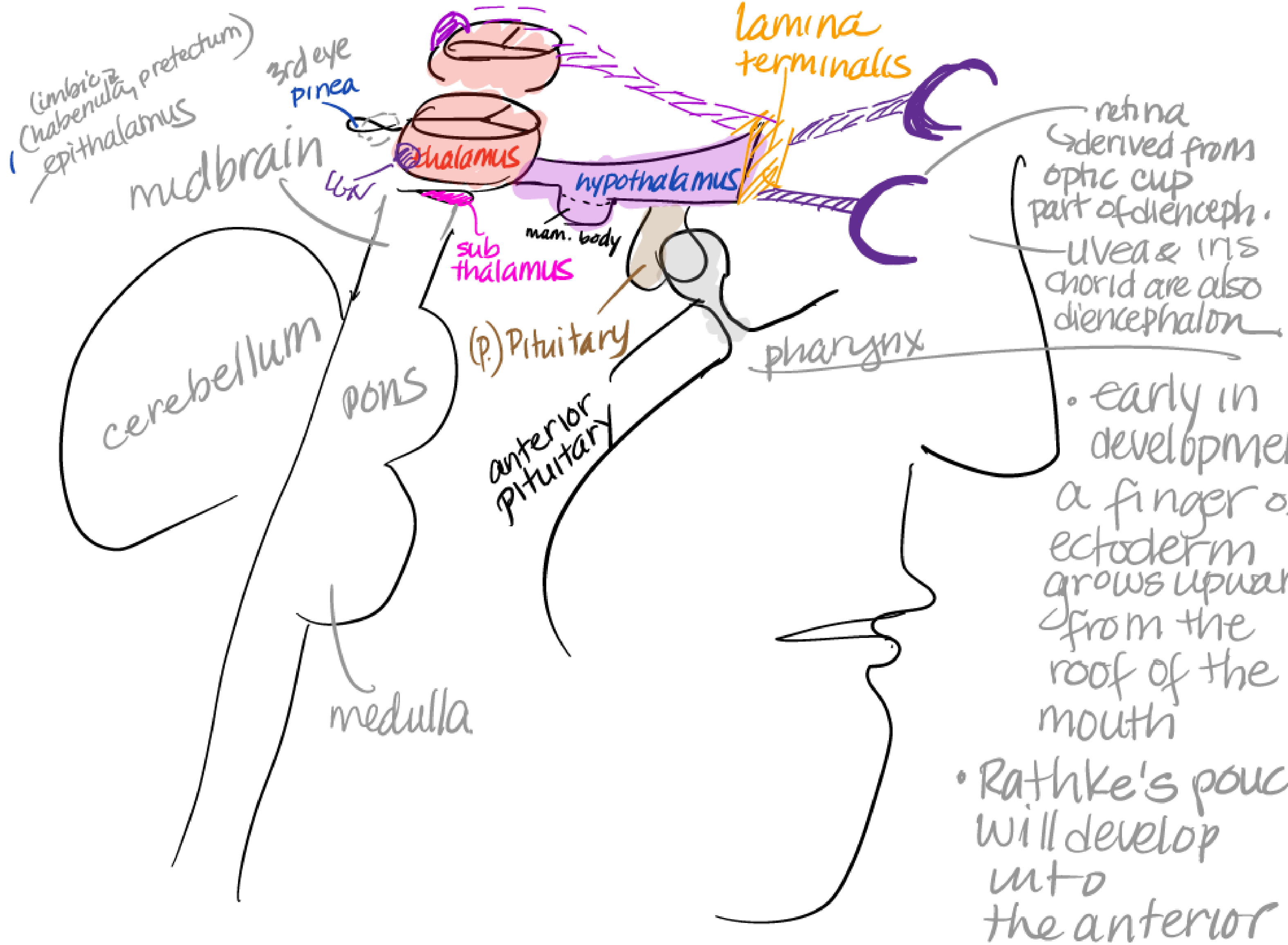
Differentiation of the telencephalon...



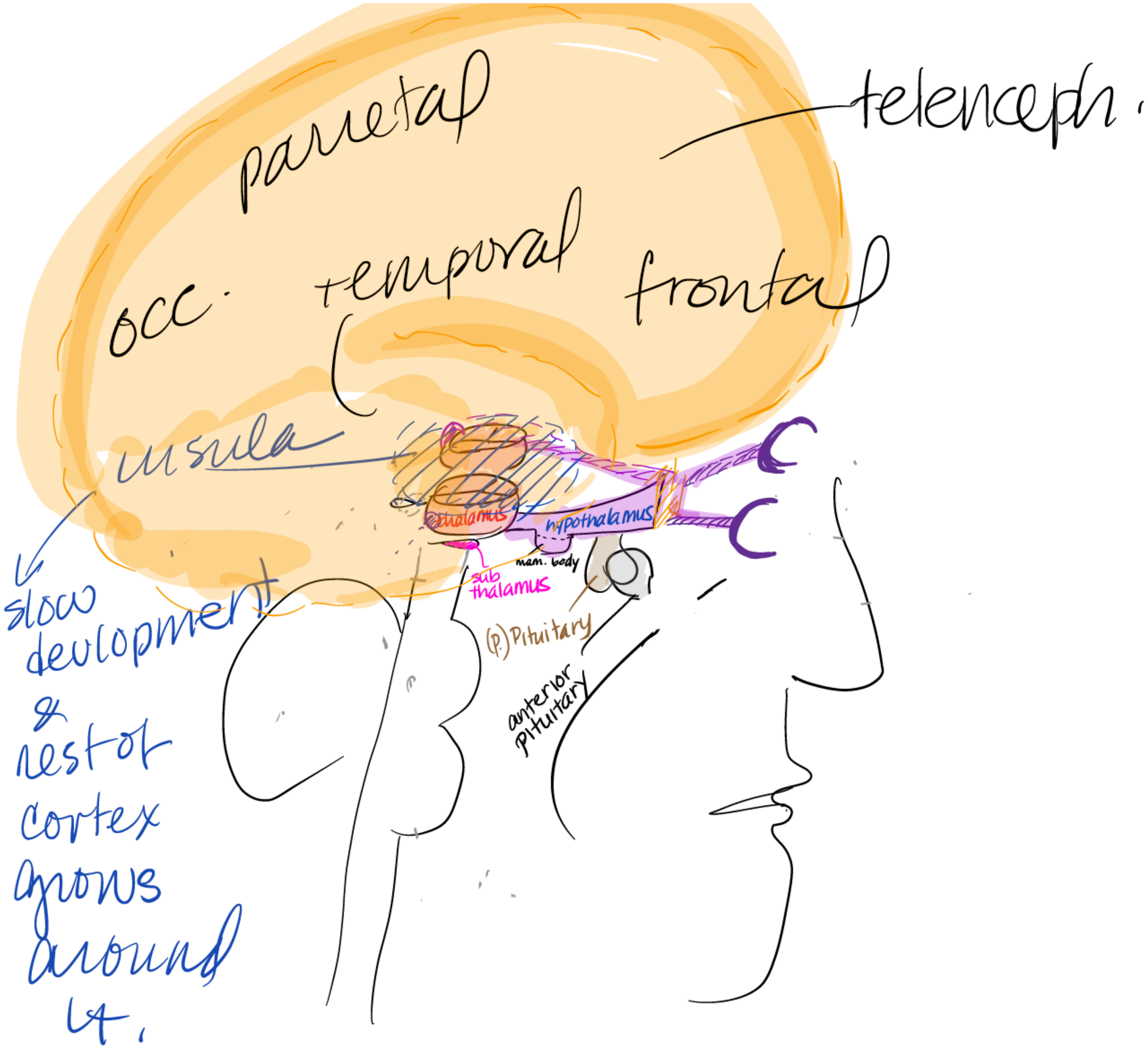
Neuroscience: Exploring the Brain, 3rd Ed, Bear, Connors, and Paradiso Copyright © 2007 Lippincott Williams & Wilkins

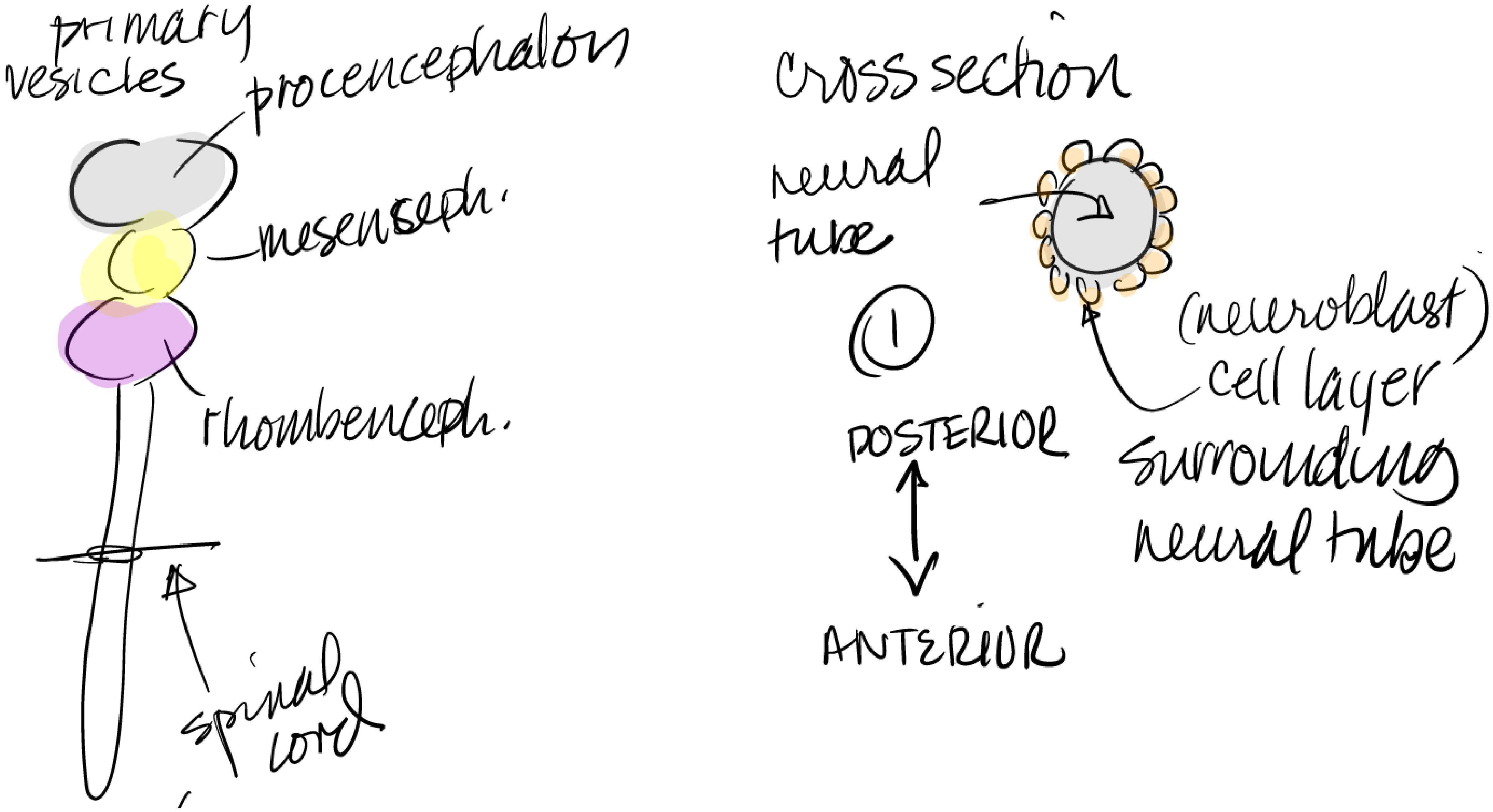

PROCENCEPHALON
telencephalon
dienceph.
midbrain
mesencephalon
pons
cerebellum
medulla
metencephalon
mylencephalon

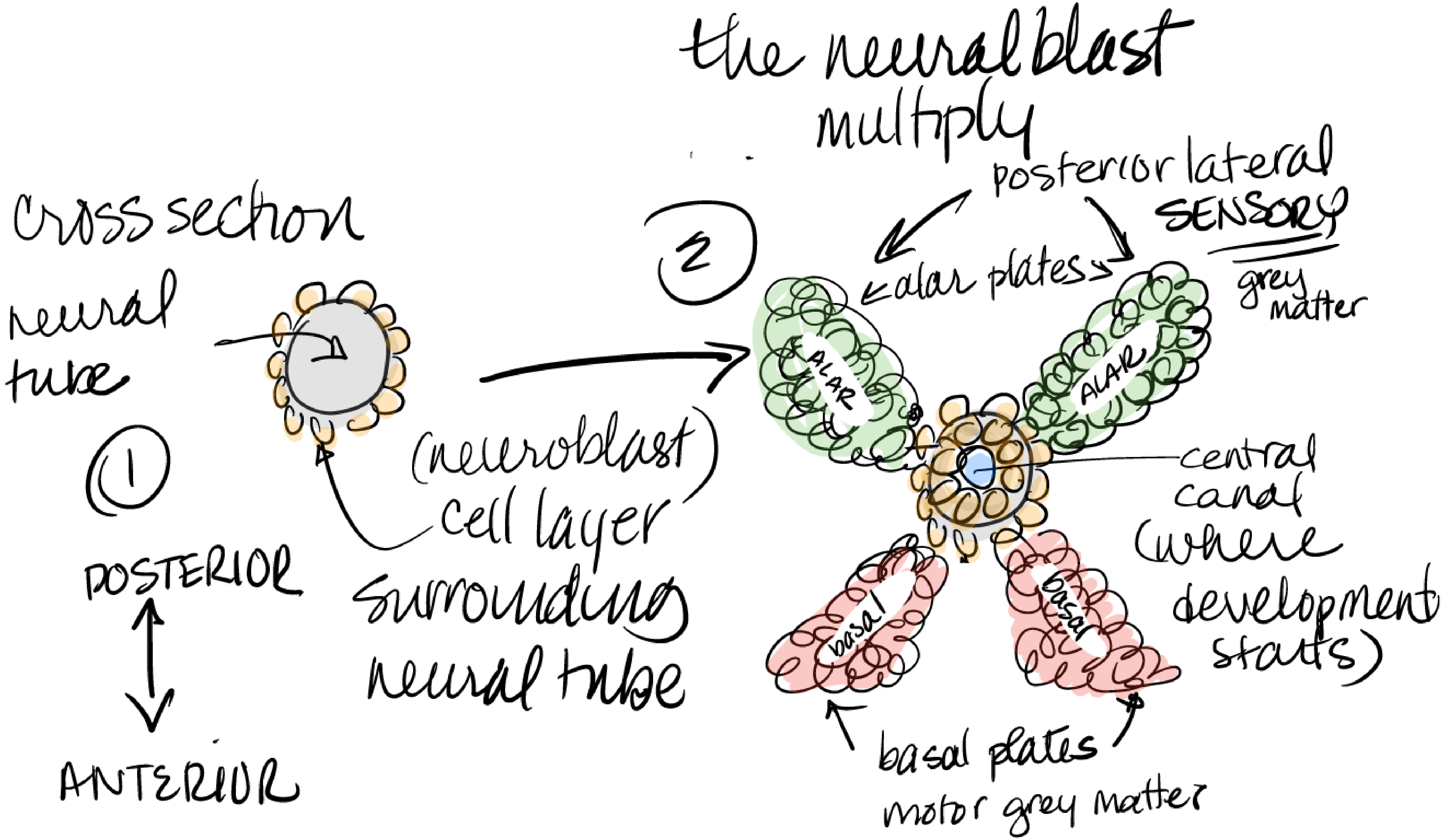

parietal
frontal
occipital
insula
diencephalon
thalamus
hypothalamus
midbrain
temporal
pons
cerebellum
medulla



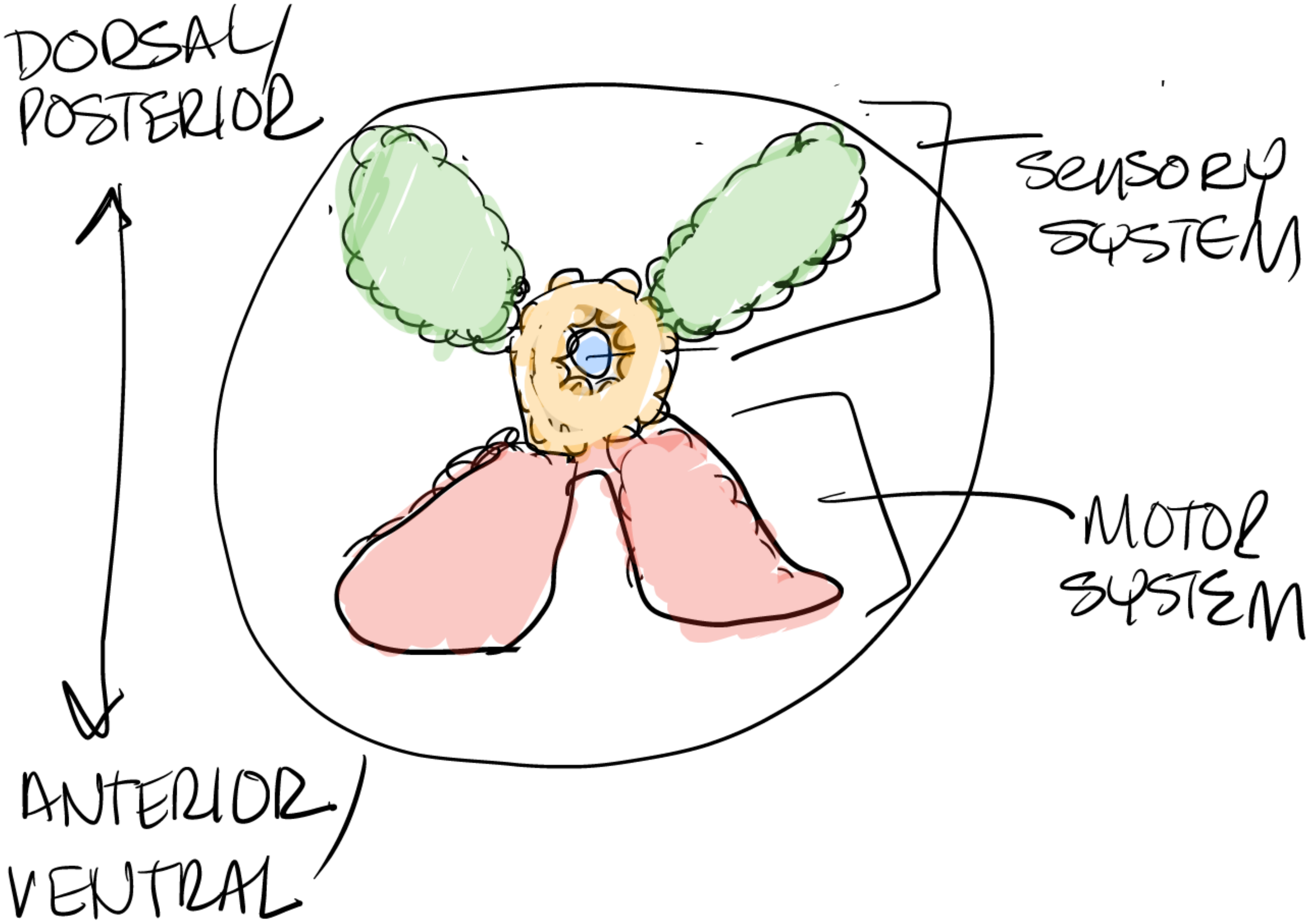
- early in development a finger of ectoderm grows upward from the roof of the mouth
- Rathke's pouch will develop into the anterior pituitary (adenohypophysis)

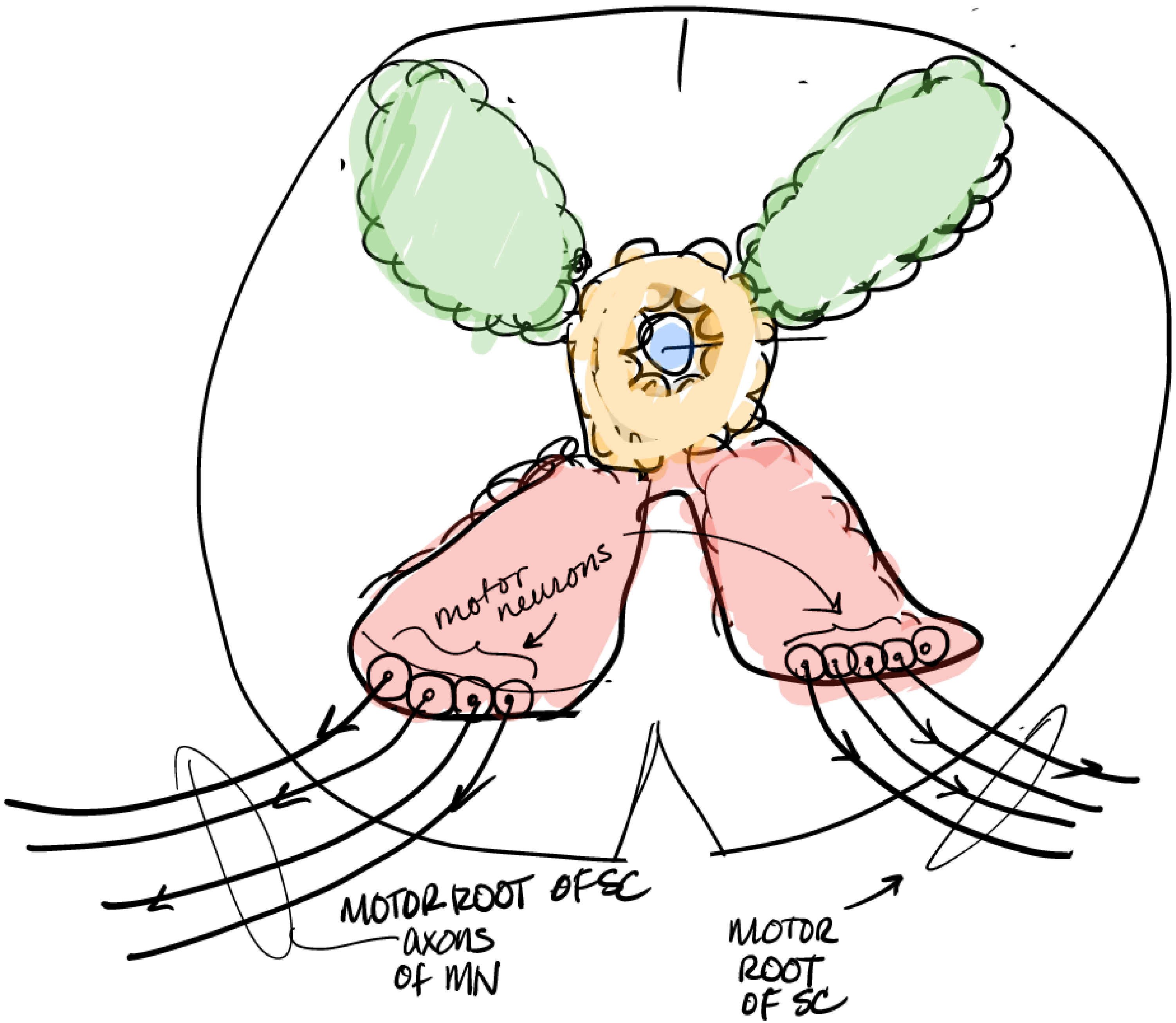

parietal
telenceph.
occ.
temporal
frontal
insula
thalamus
hypothalamus
mam. body
sub thalamus
(p.) Pituitary
anterior pituitary
slow development & rest of cortex grows around it.


primary vesicles
procencephalon
mesenseph.
rhombenceph.
spinal cord
cross section
neural tube
1
(neuroblast) cell layer surrounding neural tube
POSTERIOR
ANTERIOR

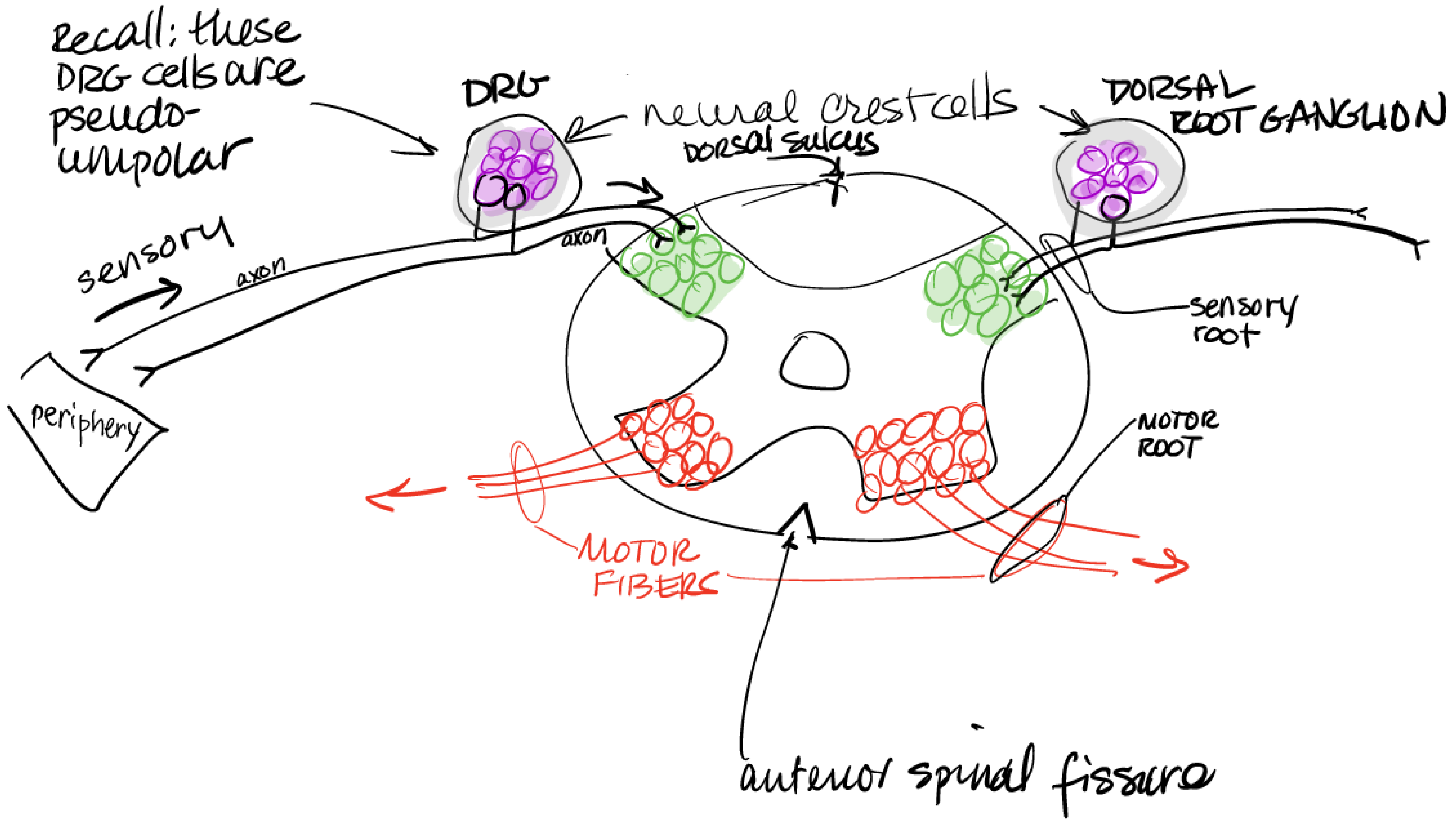


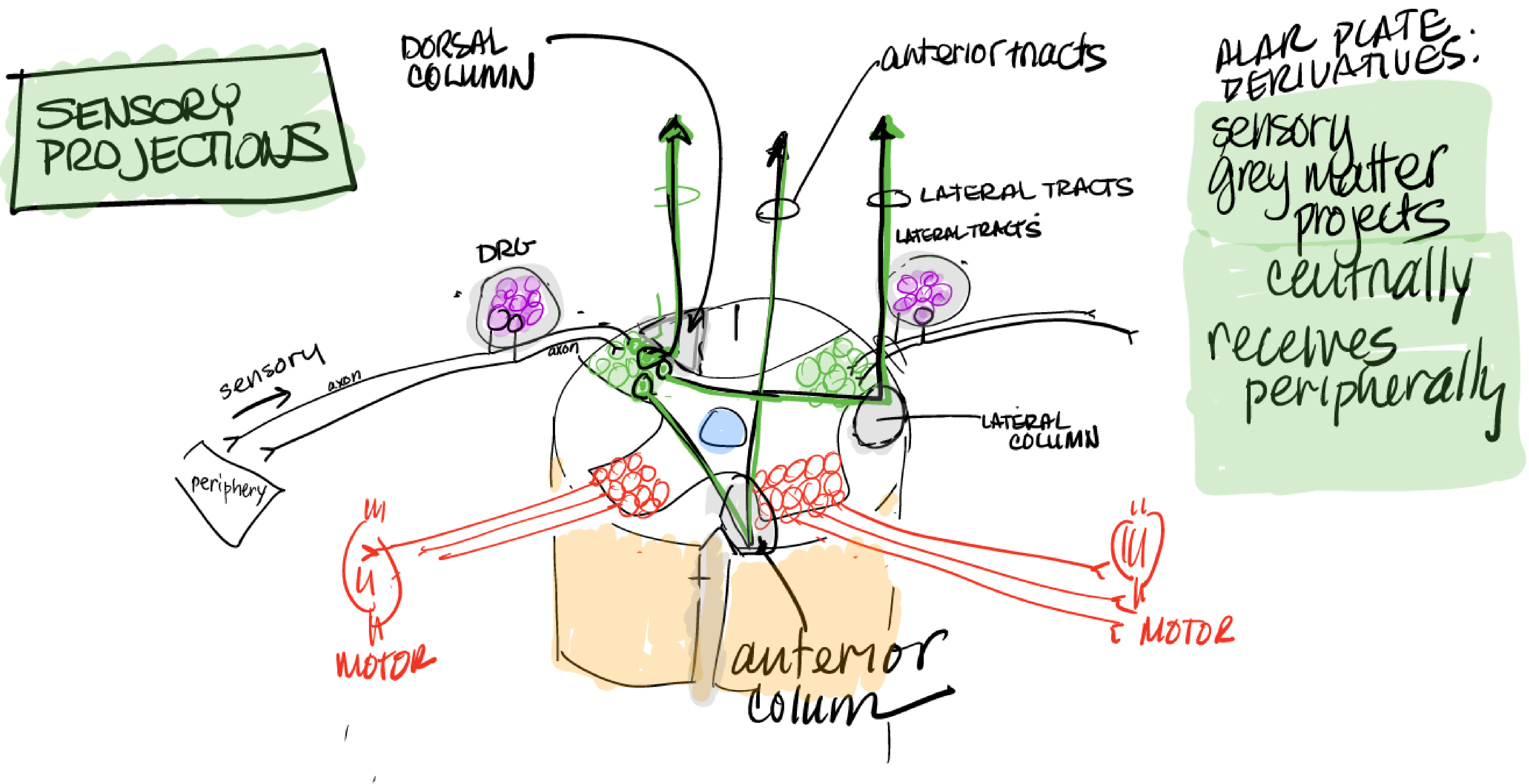
the neural blast multiply
cross section
neural tube
1
POSTERIOR
ANTERIOR
(neuroblast cell layer surrounding neural tube)
2
posterior lateral
SENSORY
grey matter
alar plates
ALAR
ALAR
central canal (where development starts)
basal
basal
basal plates
motor grey matter


DORSAL/
POSTERIOR
ANTERIOR/
VENTRAL
SENSORY
SYSTEM
MOTOR
SYSTEM

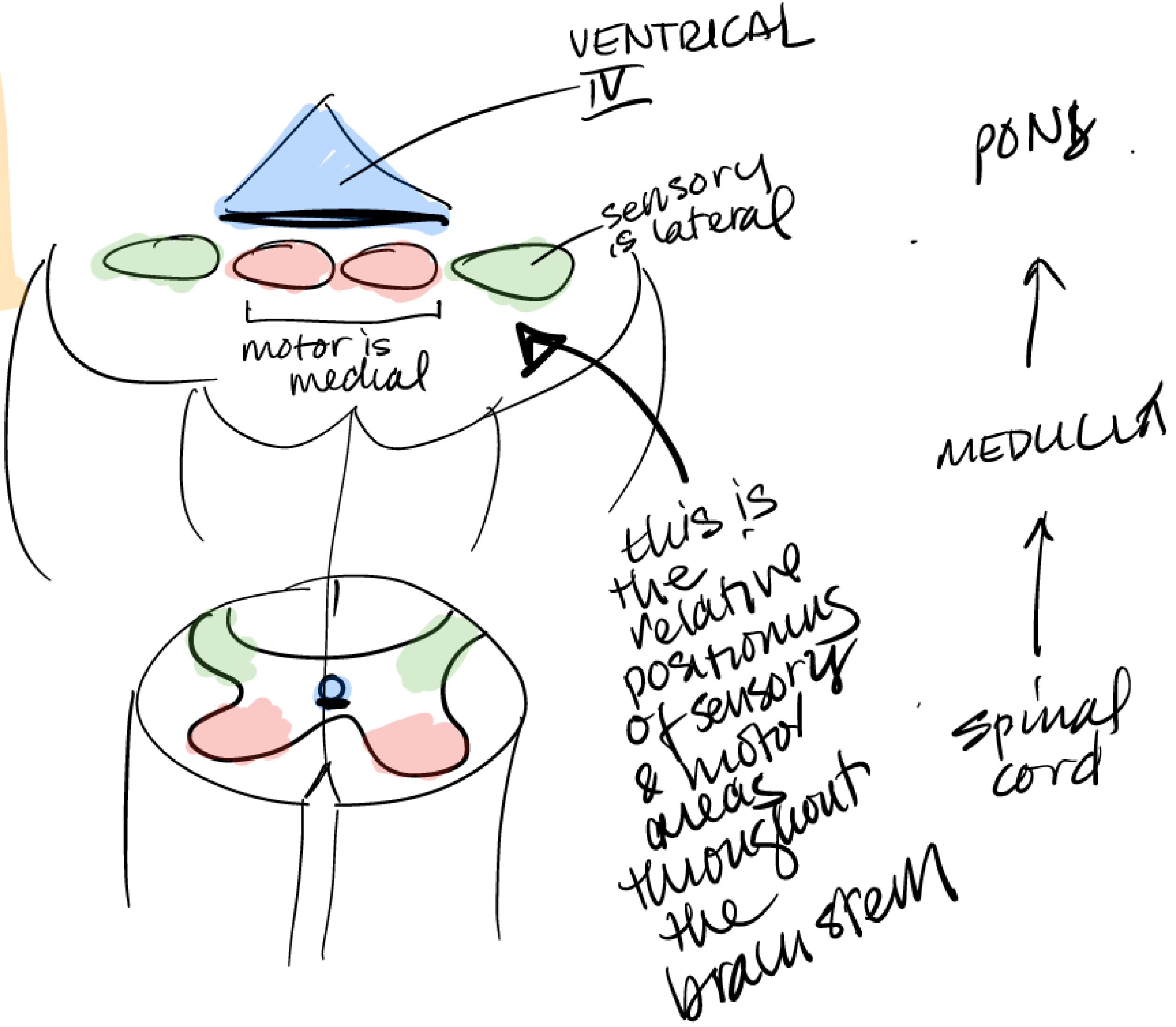


motor neurons
MOTOR ROOT OF SC
axons of MN
MOTOR ROOT OF SC


Recall: these DRG cells are pseudo-unipolar
DRG
neural crest cells
DORSAL ROOT GANGLION
DORSAL SULCUS
sensory
axon
axon
periphery
sensory root
MOTOR ROOT
MOTOR FIBERS
anterior spinal fissure

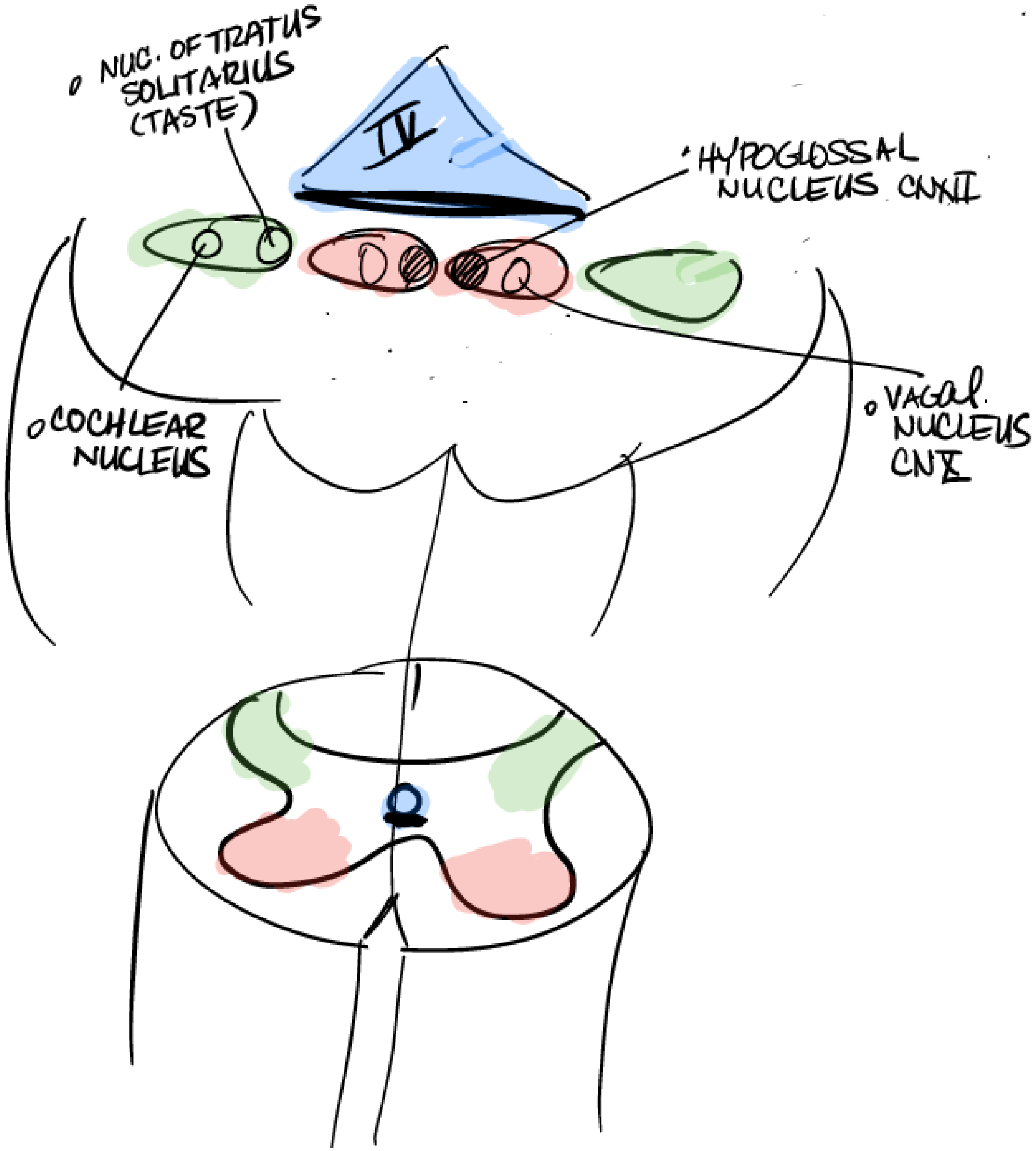

SENSORY PROJECTIONS
DORSAL COLUMN
anterior tracts
LATERAL TRACTS
LATERAL TRACTS
DRG
axon
sensory
axon
periphery
LATERAL COLUMN
MOTOR
MOTOR
anterior colum
ALAR PLATE DERIVATIVES:
sensory grey matter projects centrally
receives peripherally

Spinal Cord Relationship to BRAIN STEM:



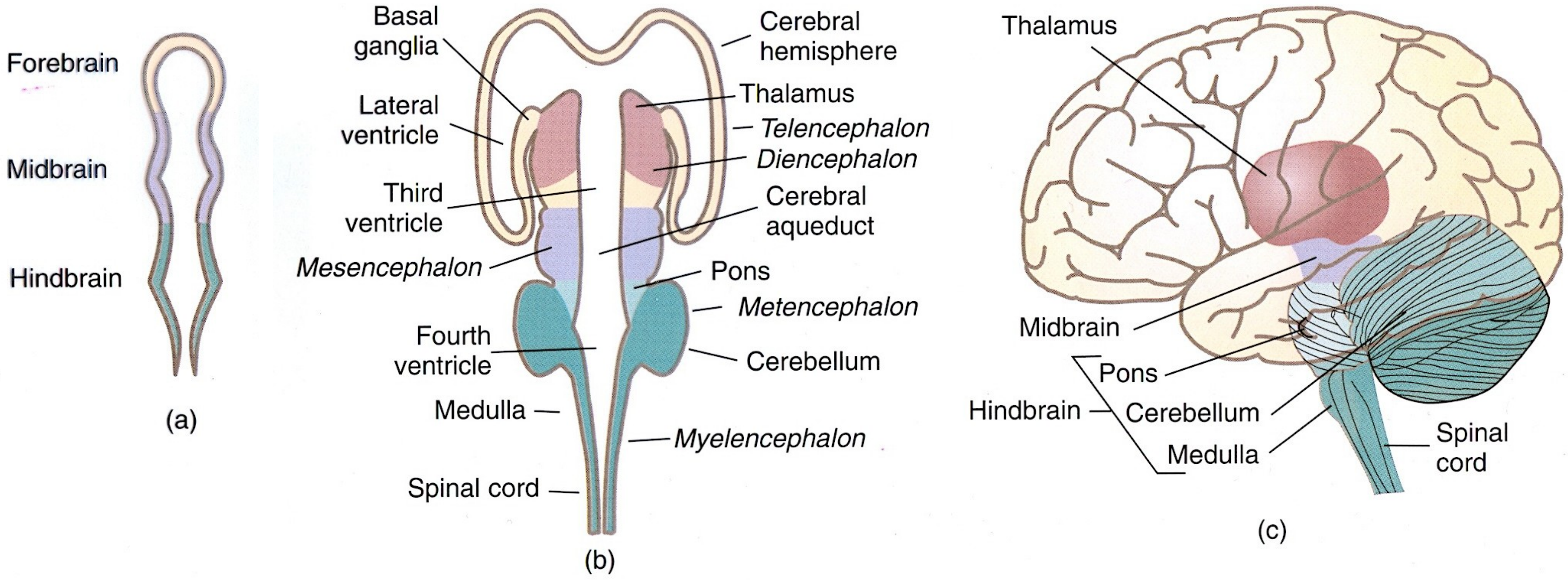
examples of sensory & motor

remember the nuclei will get fragmented because of fibers of finding (ascending descending fibers)



Neural Tube develops into

Forebrain, Midbrain & Hindbrain



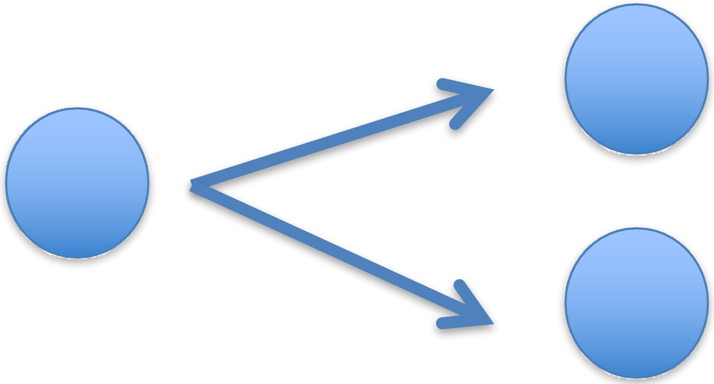
Hollow center becomes

Ventricles and **Central Canal**

Proliferation of cells

First 7 weeks: **SYMMETRICAL DIVISION**

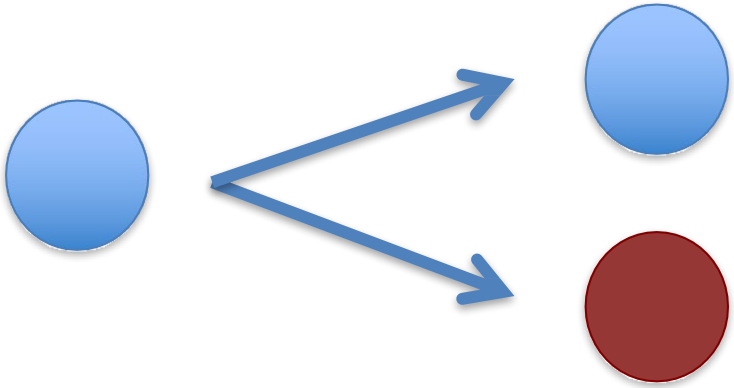
Stem Cell



2 Identical
Daughter
Cells

Then switch to **ASSYMMETRICAL DIVISION**

Stem Cell



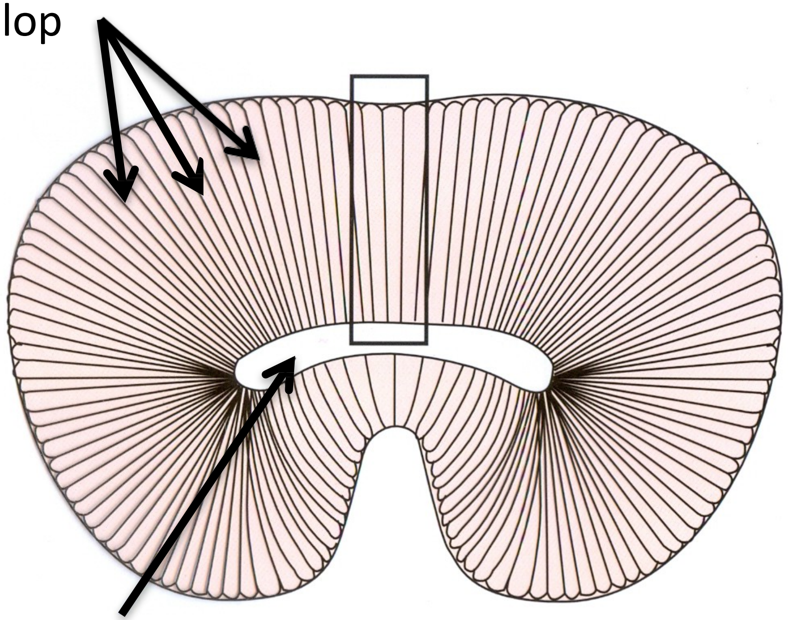
1 Stem Cell

1 Neuron
or
1 Glia

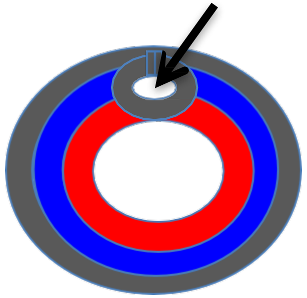
Migration

Radial Glia

One of the first types of Glia cells to develop



Ventricular Zone

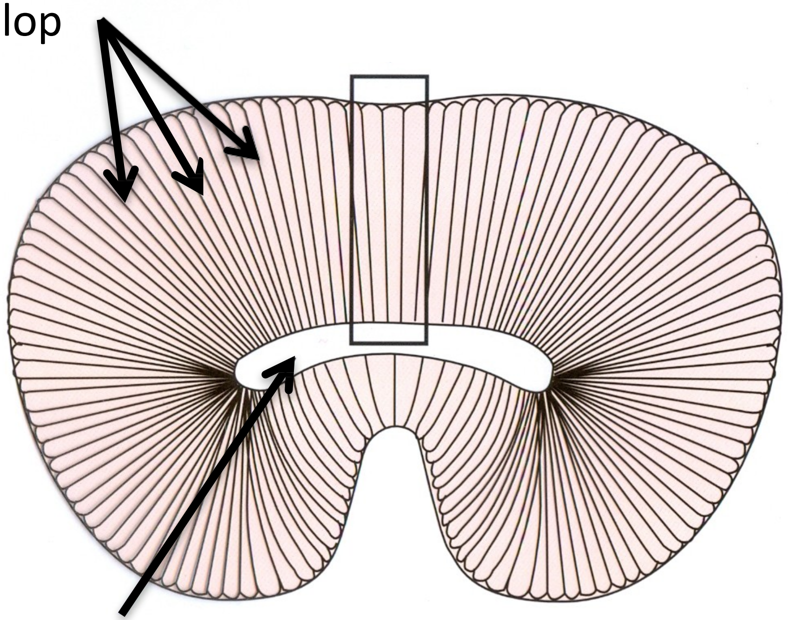


Slide from Dr. Johnson's COGS17

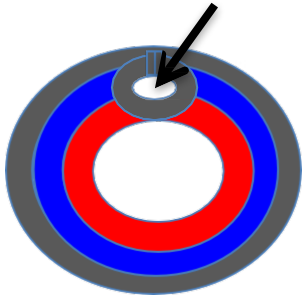
Migration

Radial Glia

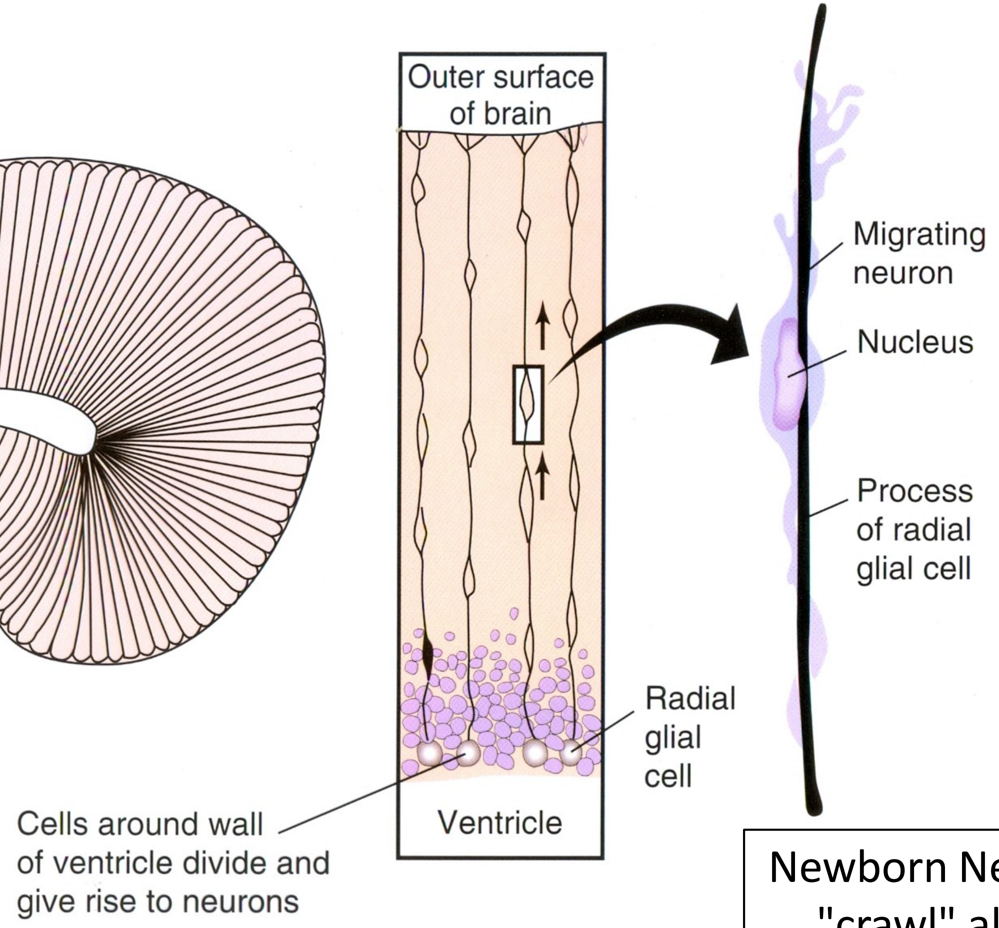
One of the first types of Glia cells to develop



Ventricular Zone



As new cells accumulate in Ventricular Zone, the Neurons start to Migrate

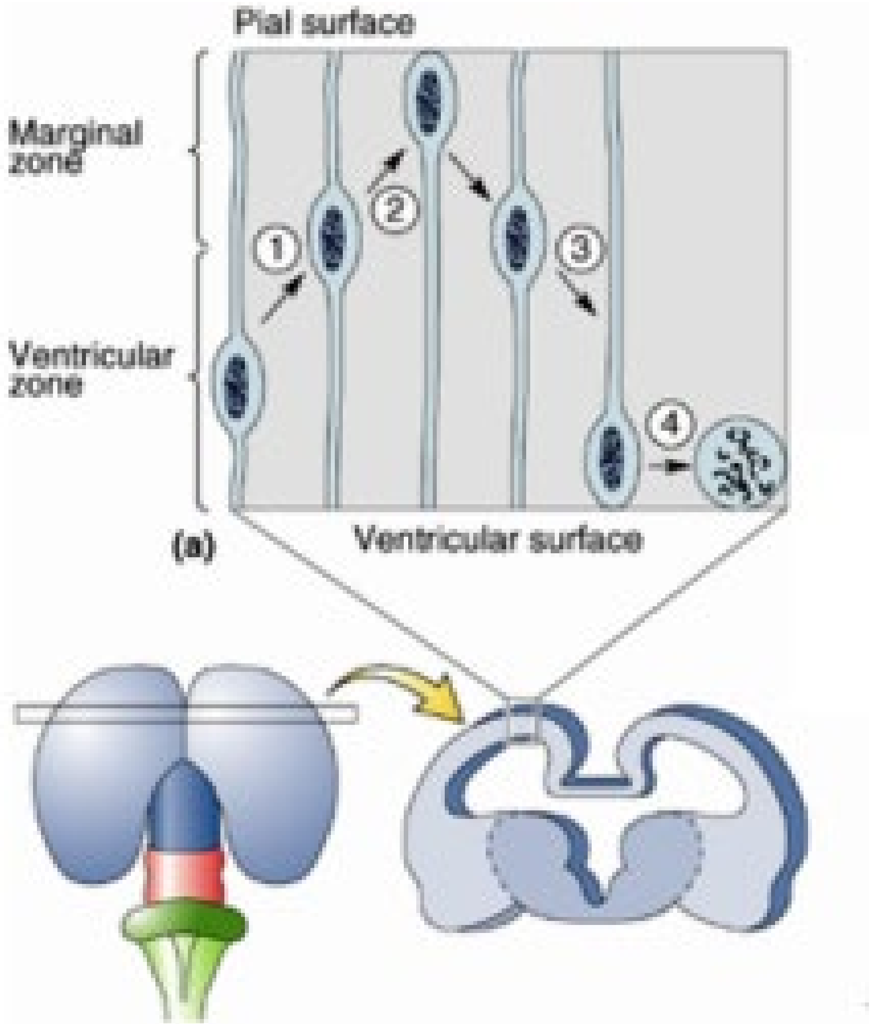


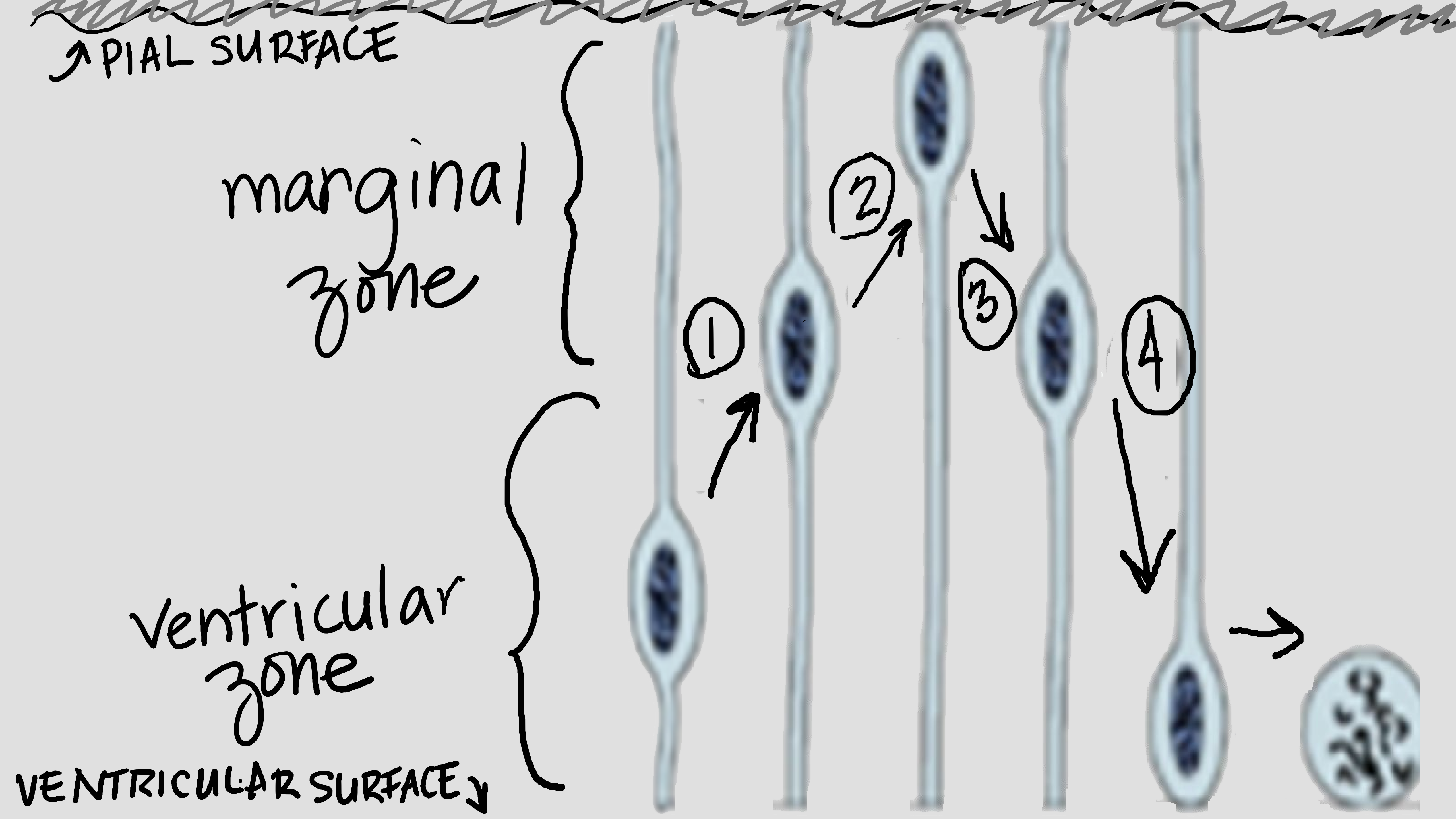
Newborn Neurons "crawl" along Radial Glia

Slide from Dr. Johnson's COGS17

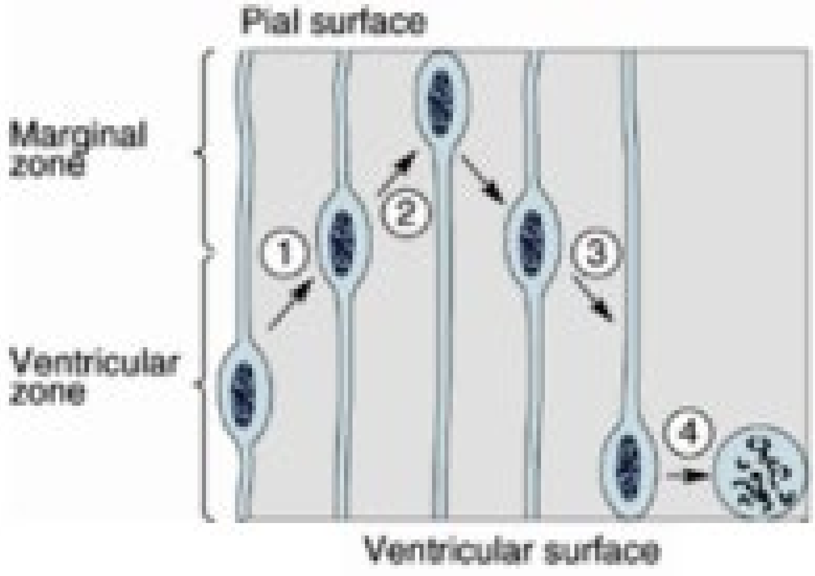
… there were neurons (and glia)…walls of vesicles

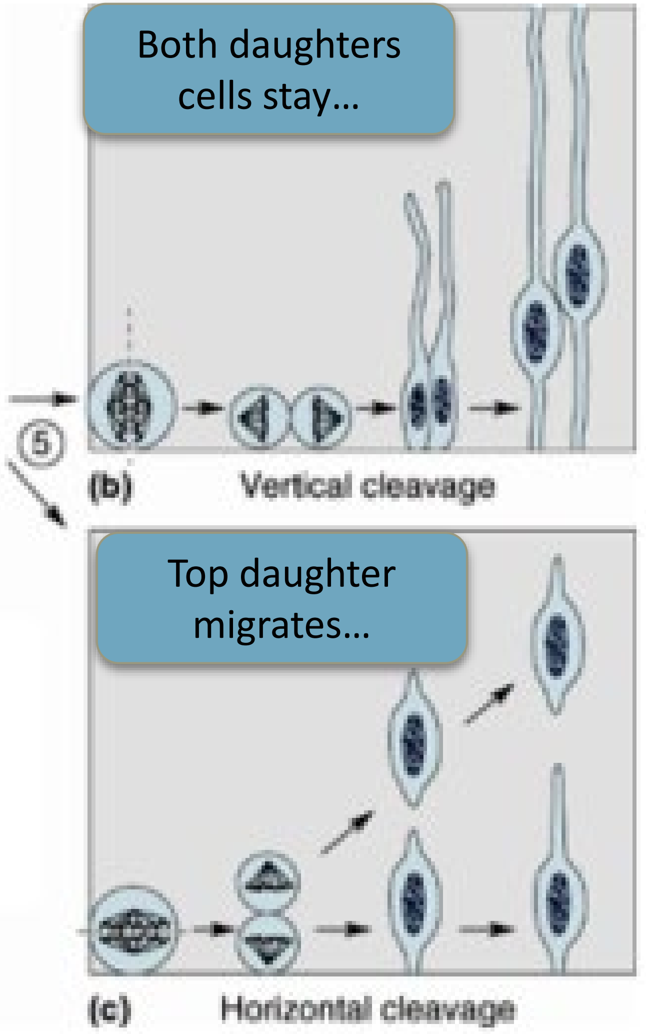
- Brain develops from the walls of the five vesicles.
  - Early development – there are two layers that make up the walls of the vesicle:
    - Marginal zone
    - Ventricular zone




PIAL SURFACE
marginal zone
ventricular zone
VENTRICULAR SURFACE
1
2
3
4

… the five (prolific) positions…

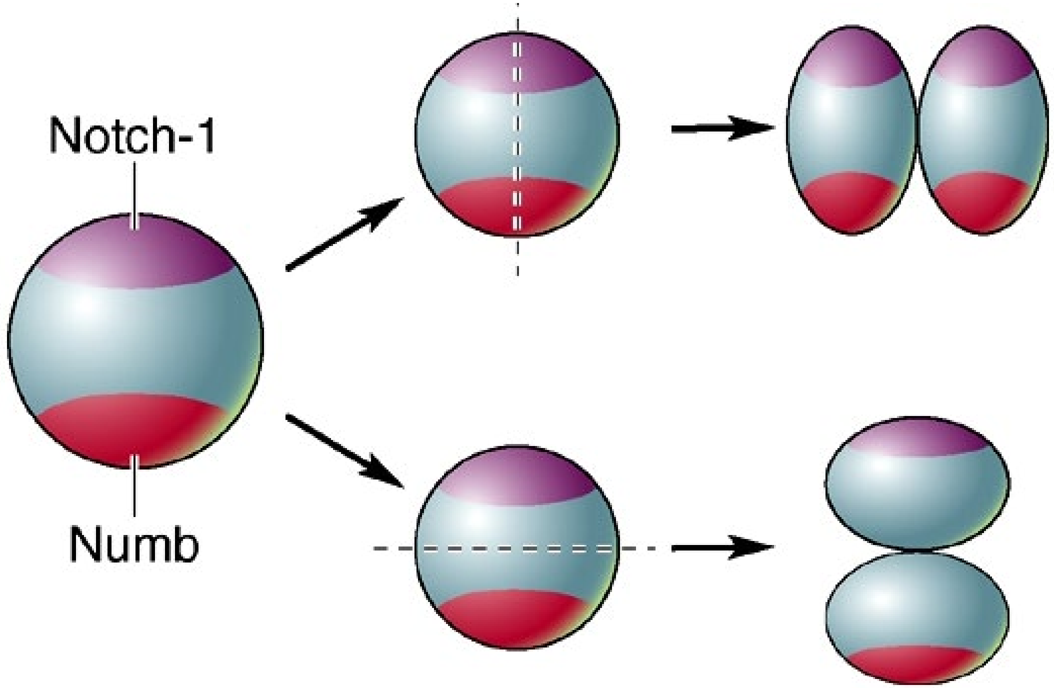


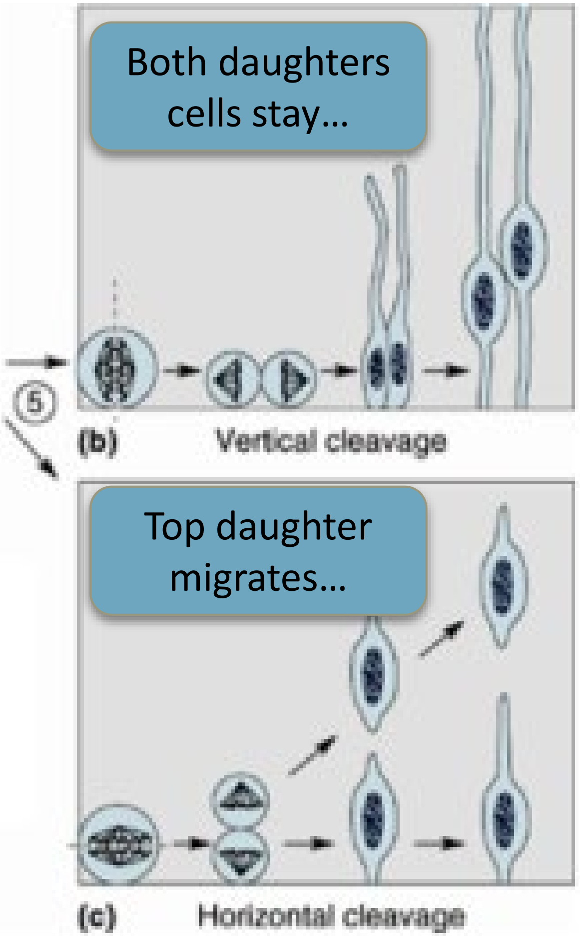


The positions:

- First position: Extension
- Second position: Migration – DNA replication
- Third position: Return to ventricular surface
- Fourth position: Retraction
- Fifth position: Division (and … stay or go?)

… and your fate is… determined by the cleavage plane!!



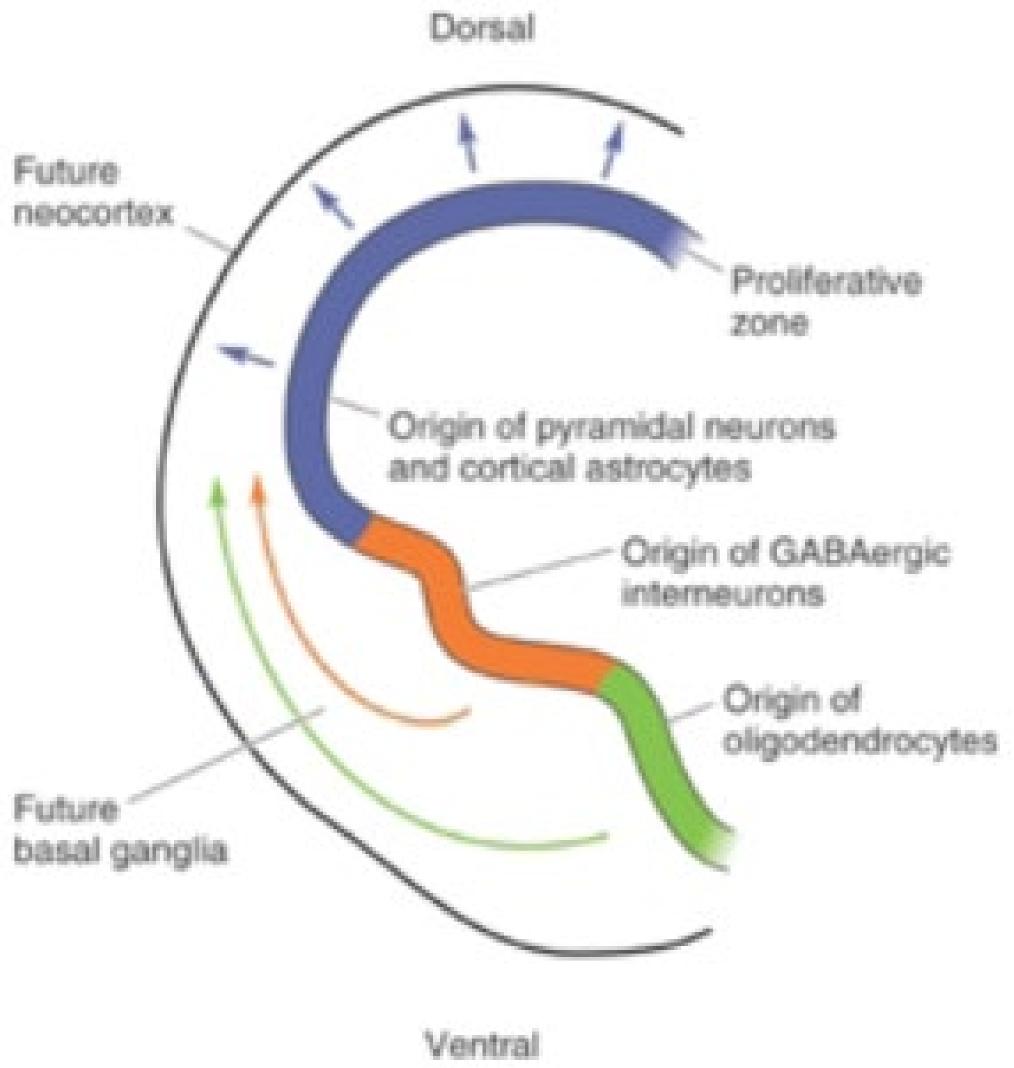


Cleavage plane

- Determine distribution of transcription factors are passed on to the daughter cells

Where do the migrating daughters go?

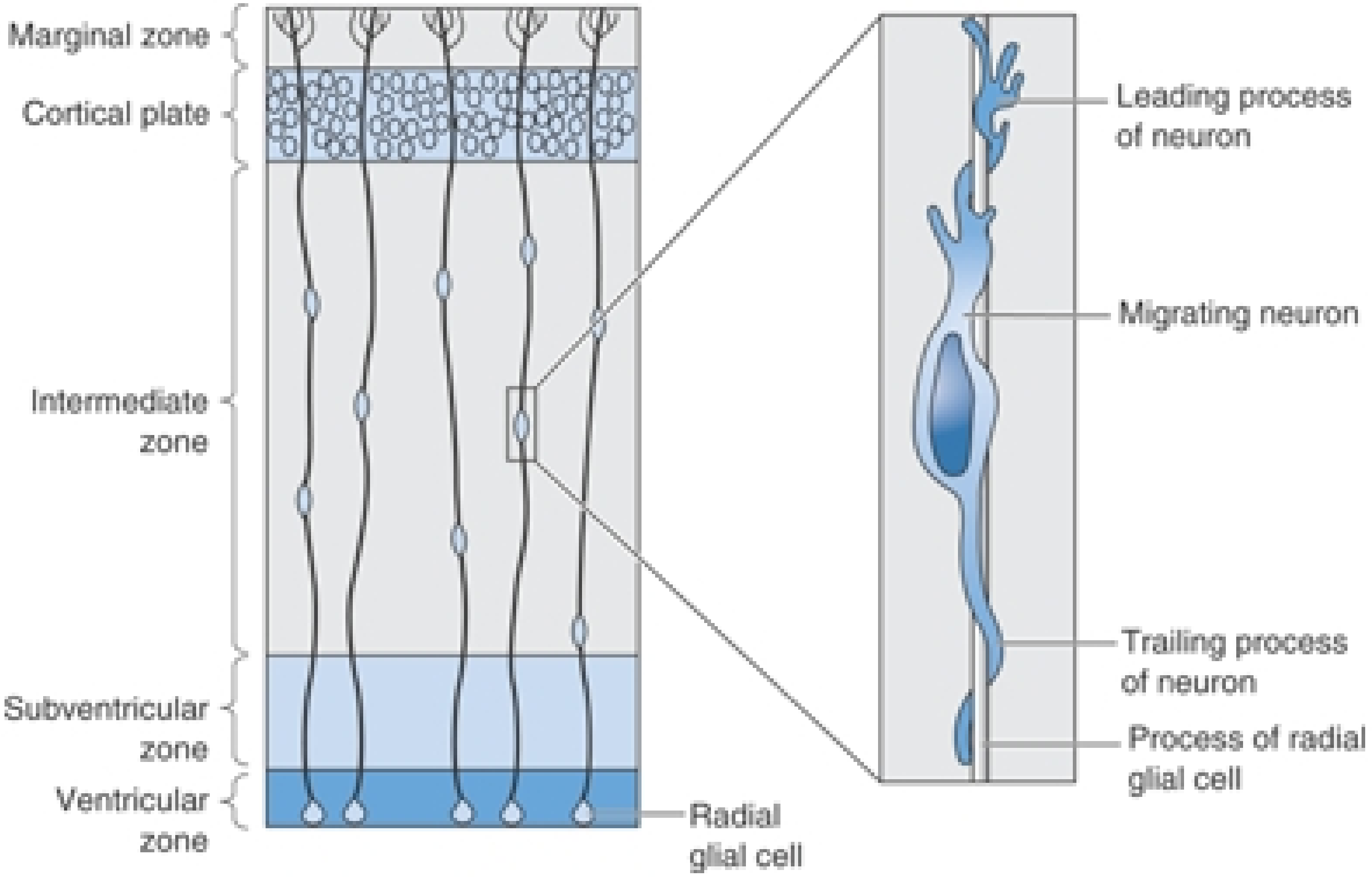
The ultimate fate of the migrating daughter cell is determined by a combination of factors, including the age of the precursor cell, its position within the ventricular zone and its environment at the time of division.



Depends on **where** they were born!

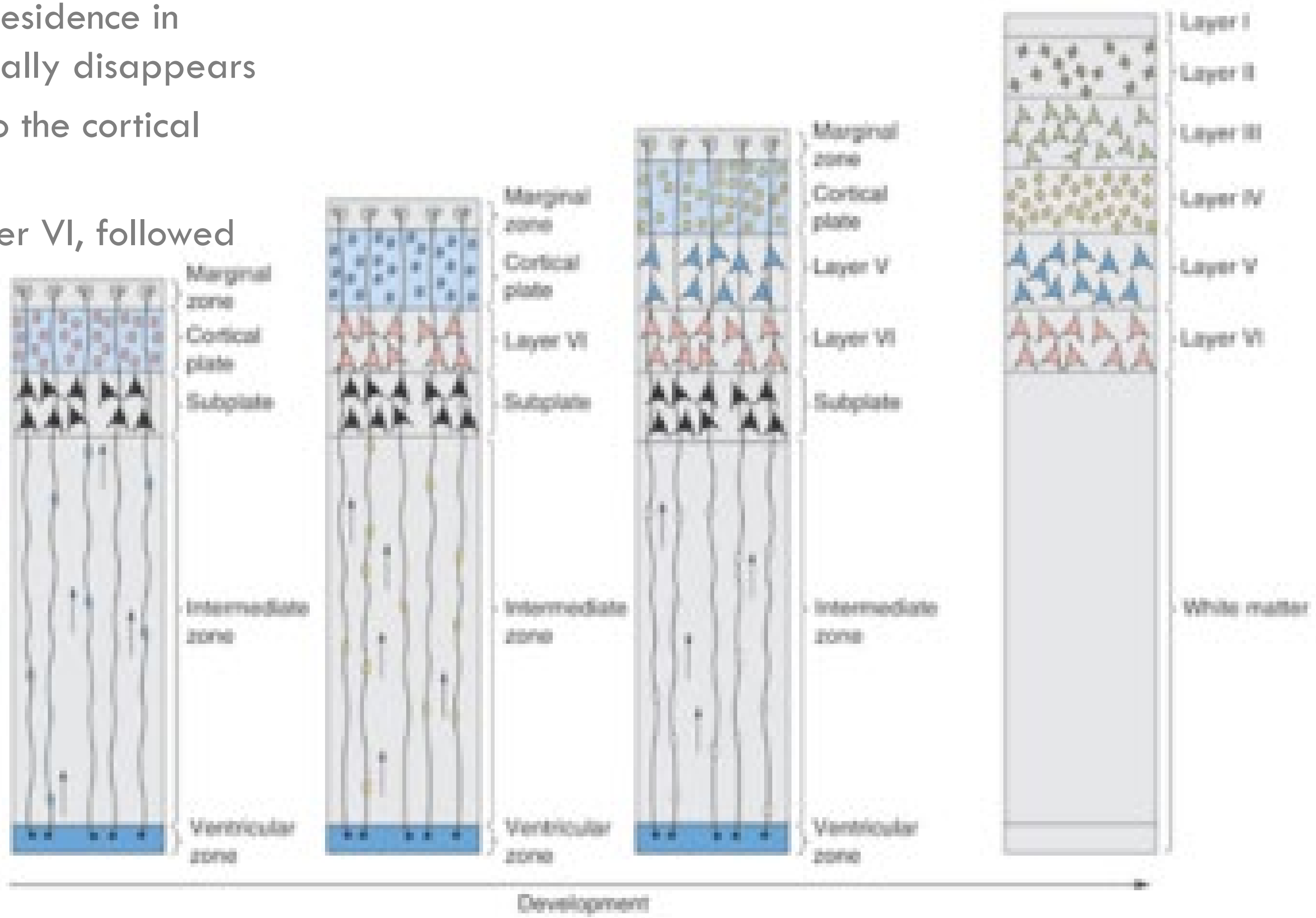
...slithering along the radial glial cells...

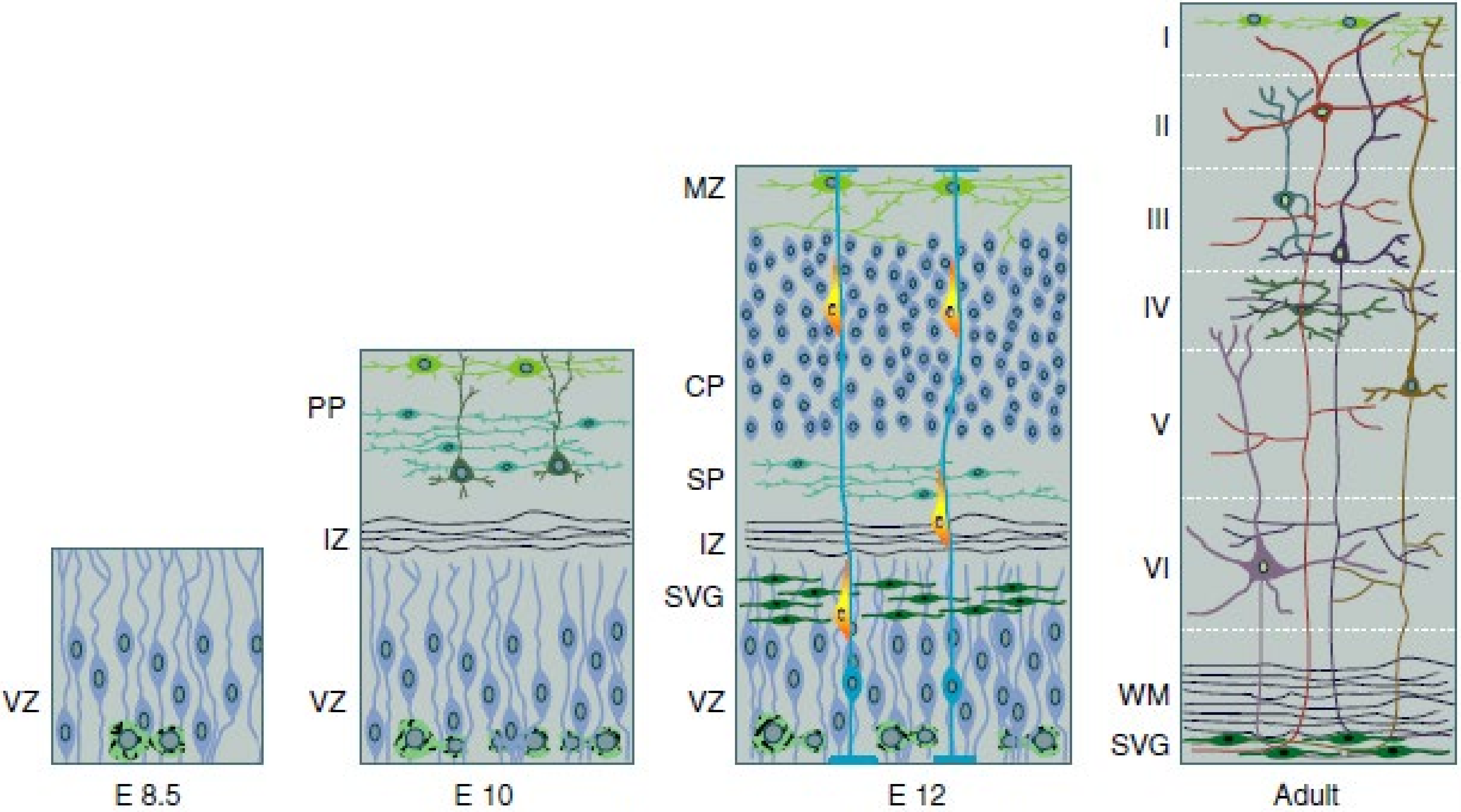
- Pyramidal cells and astrocytes migrate **vertically from ventricular zone** by moving along thin radial glial fibers
- Inhibitory **interneurons and oligodendroglia generate** from a different site and **migrate laterally**
-



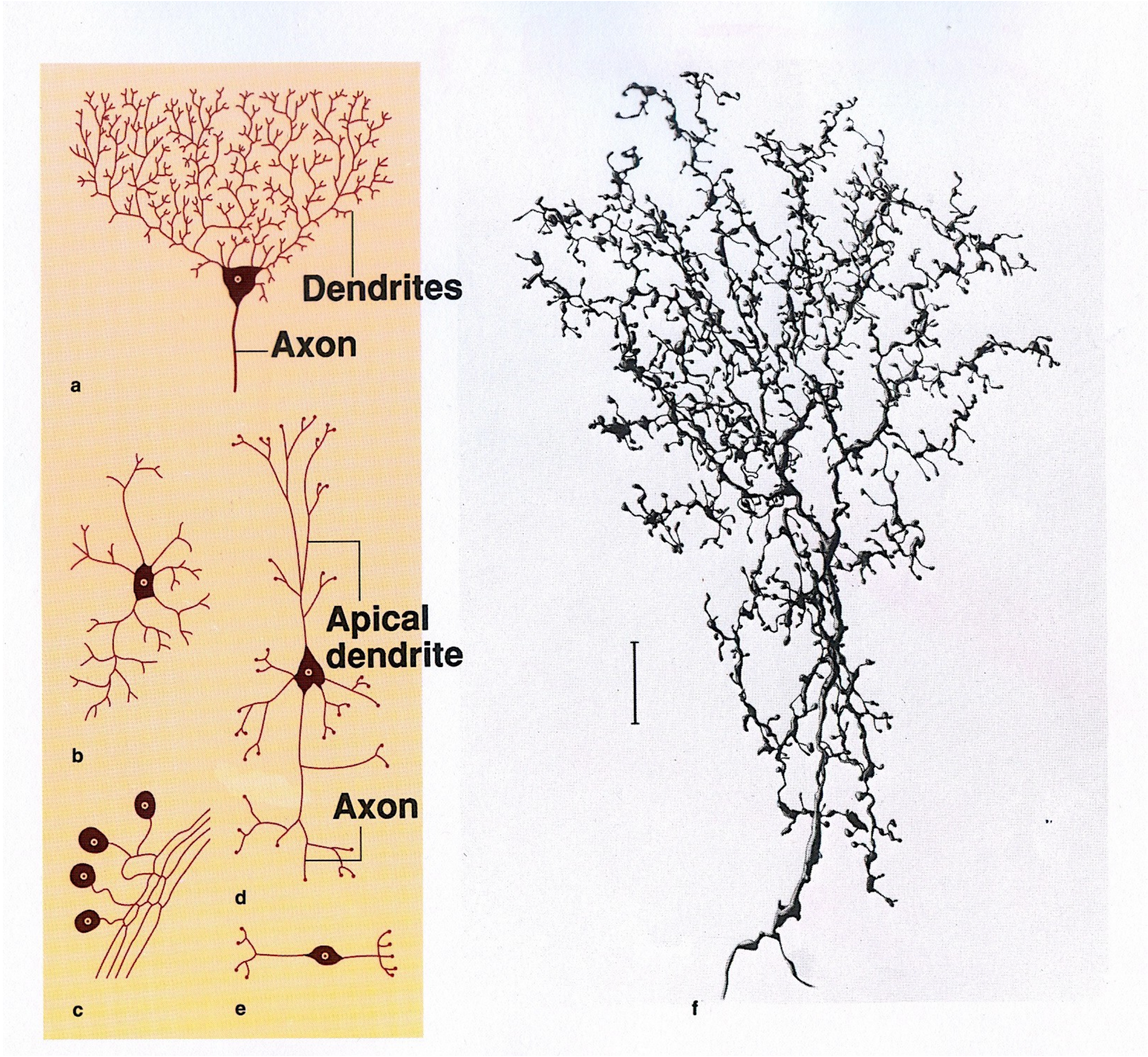
… Oh the places they'll go!

- First cells to migrate take up residence in "subplate" layer which eventually disappears
- Next cells to divide migrate to the cortical plate
- The first to arrive become layer VI, followed V, IV, and so on: "inside out"




VZ
E 8.5
PP
IZ
VZ
E 10
MZ
CP
SP
IZ
SVG
VZ
E 12
I
II
III
IV
V
VI
WM
SVG
Adult

Differentiation



Once in place,
Neurons begin to
differentiate
into a wide variety
of cell types

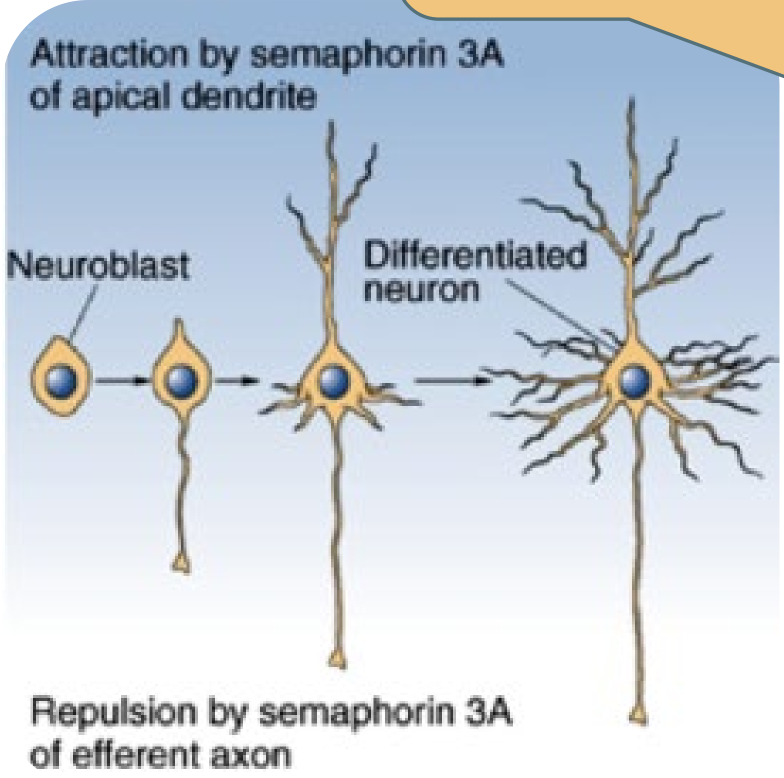
Influenced by
Cell Autonomous
(genetic) and
Induction
(environmental)
factors

Slide from Dr. Johnson's COGS17

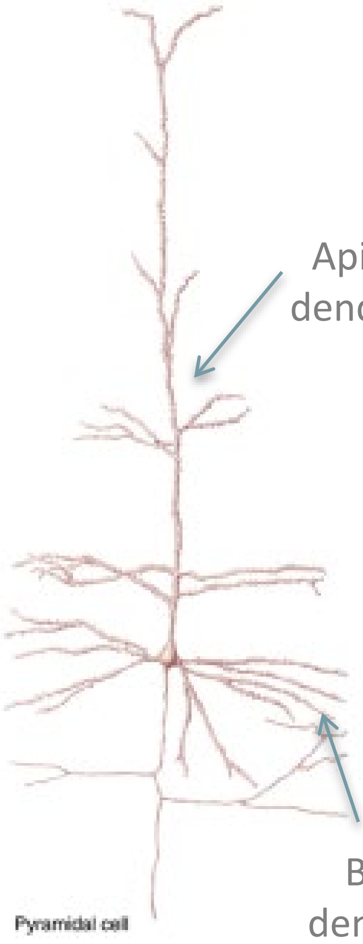
...go forth and differentiate...(nurture nature, again!)

Cortical pyramidal cells are pre-programmed for the characteristic dendritic architecture – but require **intercellular** communication for the **apical dendrite** to grow towards the pia.

Cell takes the appearance and characteristics of a neuron after reaching its destination but programming is a combination of genes and environment!

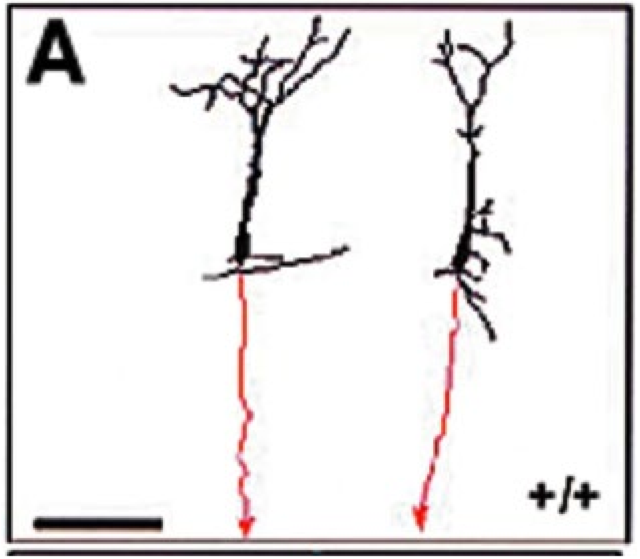


The differentiation of a neural precursor cell into a pyramidal neuron. Semaphorin 3A, a protein secreted by cells in the marginal zone, repels the growing axon and attracts the growing apical dendrite, giving the pyramidal neuron its characteristic polarity.

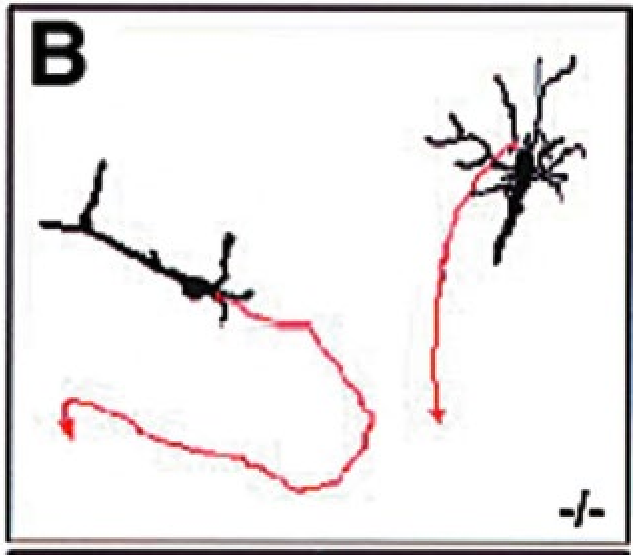


Differentiation is the consequence of a specific **spatiotemporal** pattern of gene expression.

Semaphorin 3A helps guide the initial outgrowth of pyramidal axons in the cortex.



(A) Pyramidal neurons in perinatal wild-type (+/+) mice. Their axons extend directly toward the deeper white matter (bottom) while their dendrites stretch toward the pial surface (top).

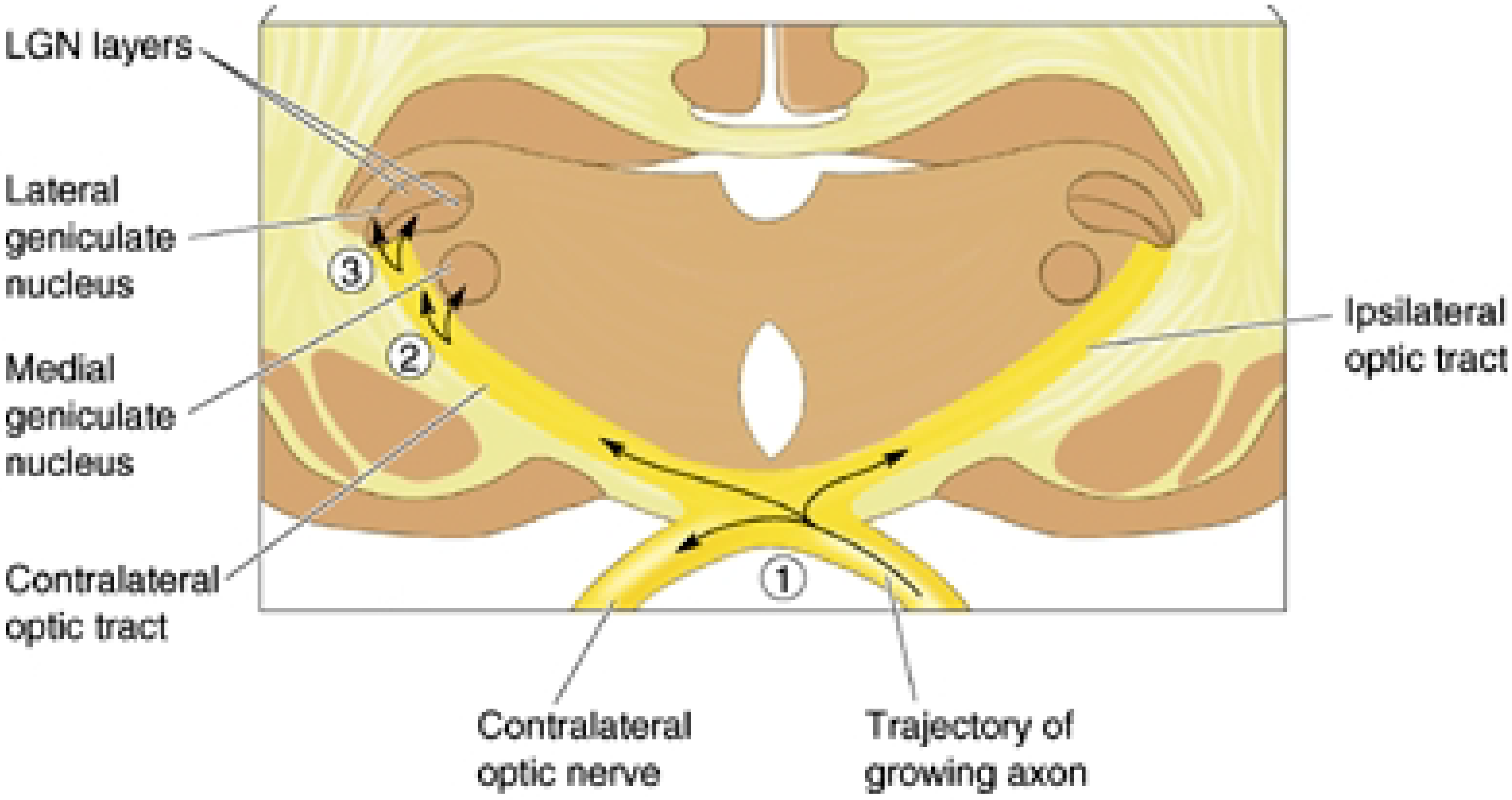


In semaphorin 3A mutant mice, pyramidal cells are appropriately polarized, but their axons and dendrites are not oriented correctly.

Polleux *et al*. (1998).

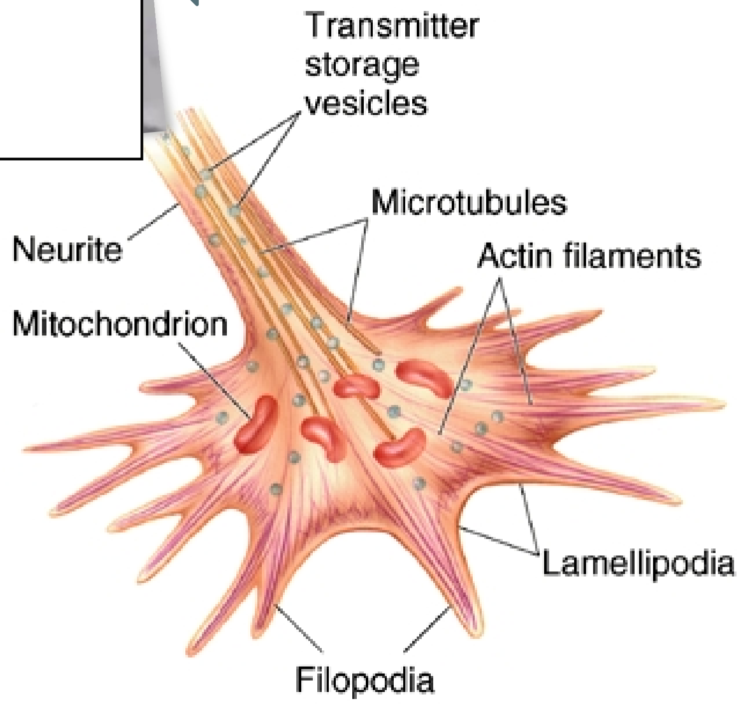
...the three phases to pathway formation...

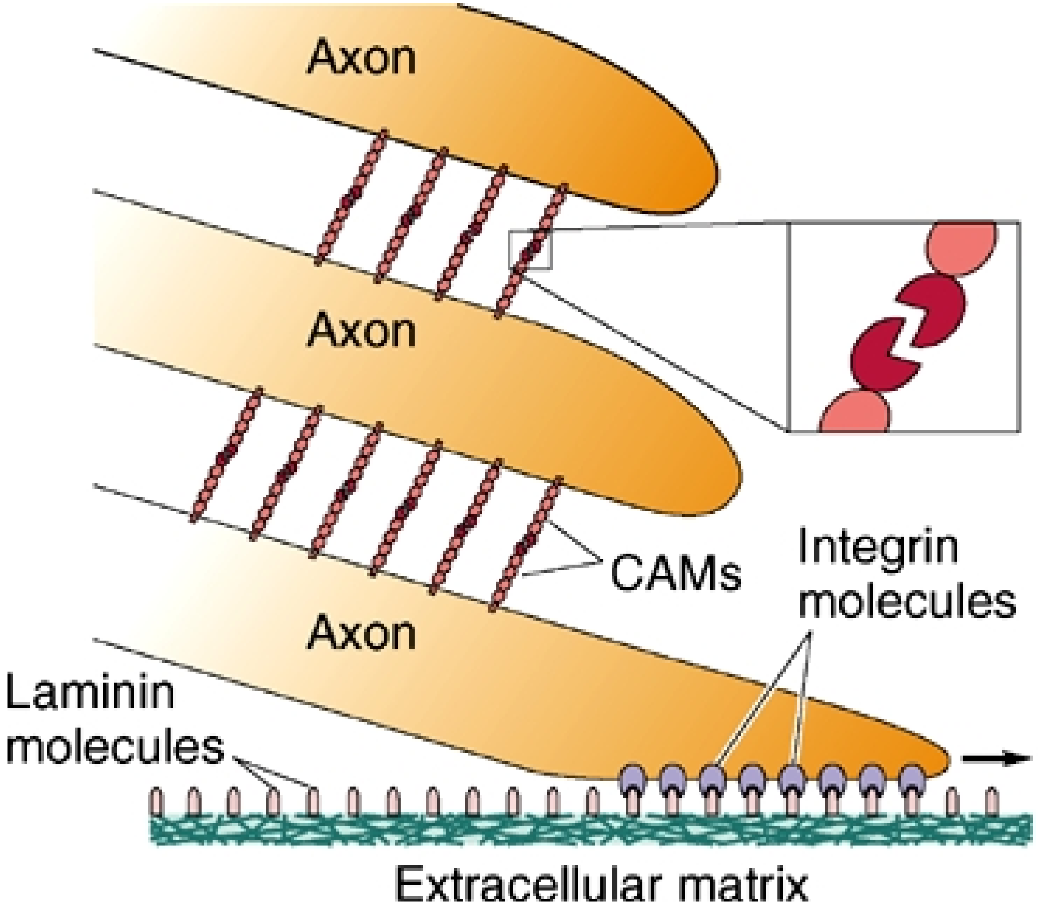
1. Axon must choose the correct PATH
2. Axon must choose the correct TARGET to innervate
3. ADDRESS selection – axon must synapse at the right spot!



...the growing axon...Growth cone: Growing tip of a neurite

Watch it in action

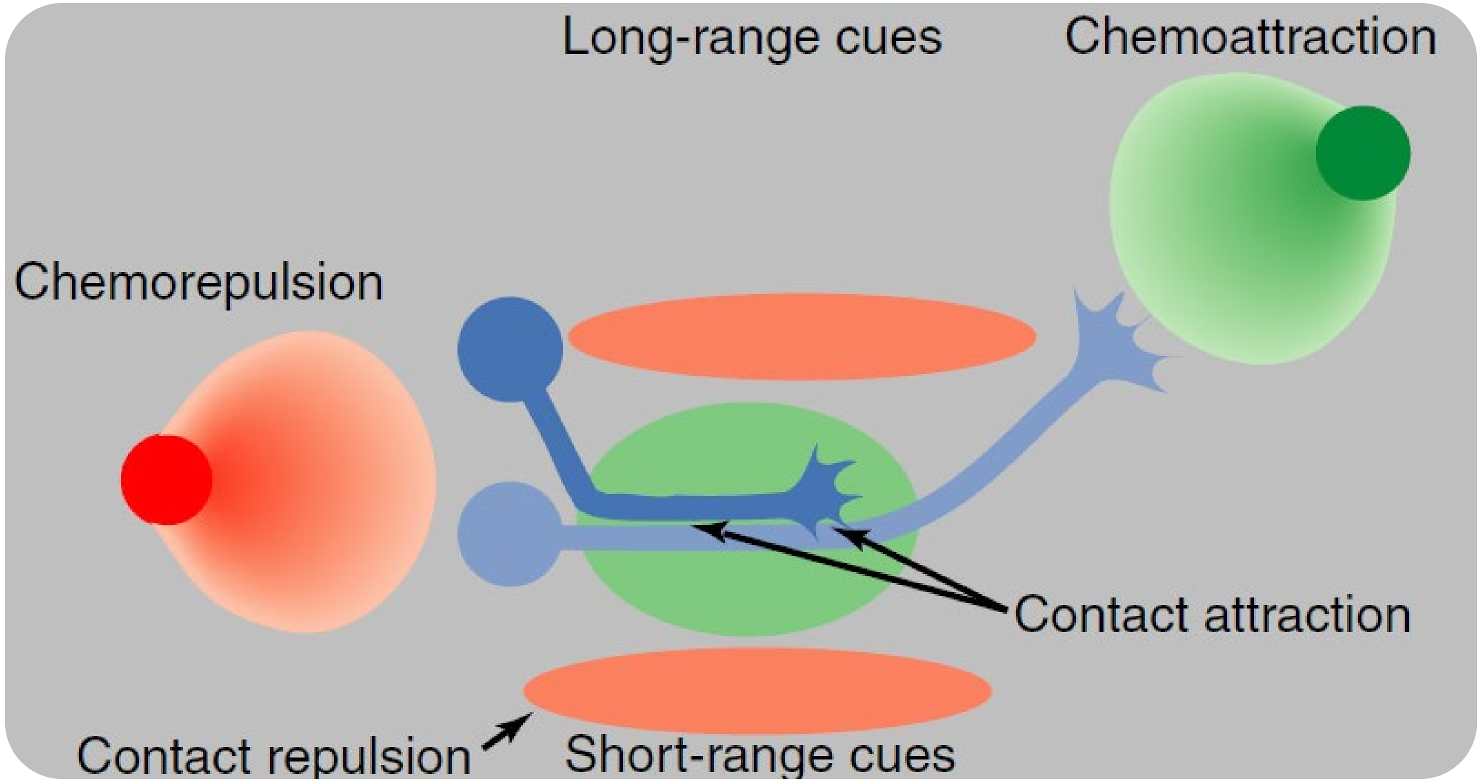




4 Types of guidance mechanisms

Contact attraction & Chemoattraction

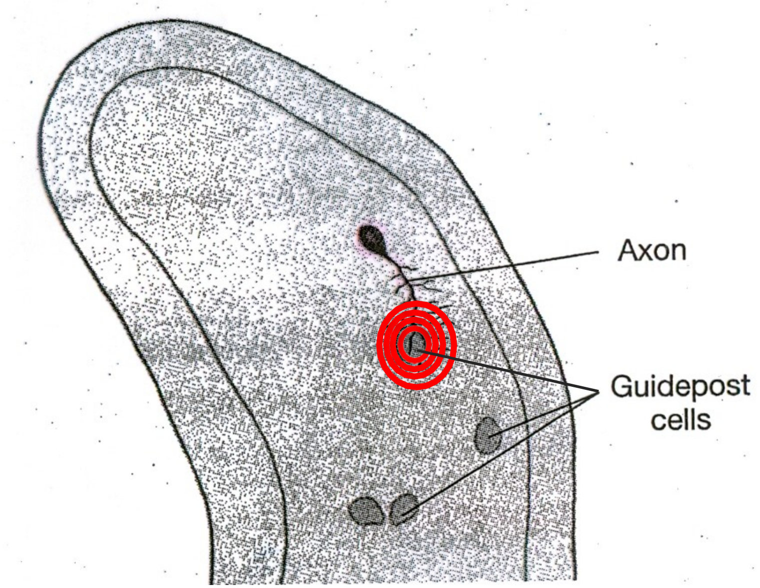
Contact repulsion & Chemorepulsion



Tessier-Lavigne and Goodman (1996).

Synaptogenesis

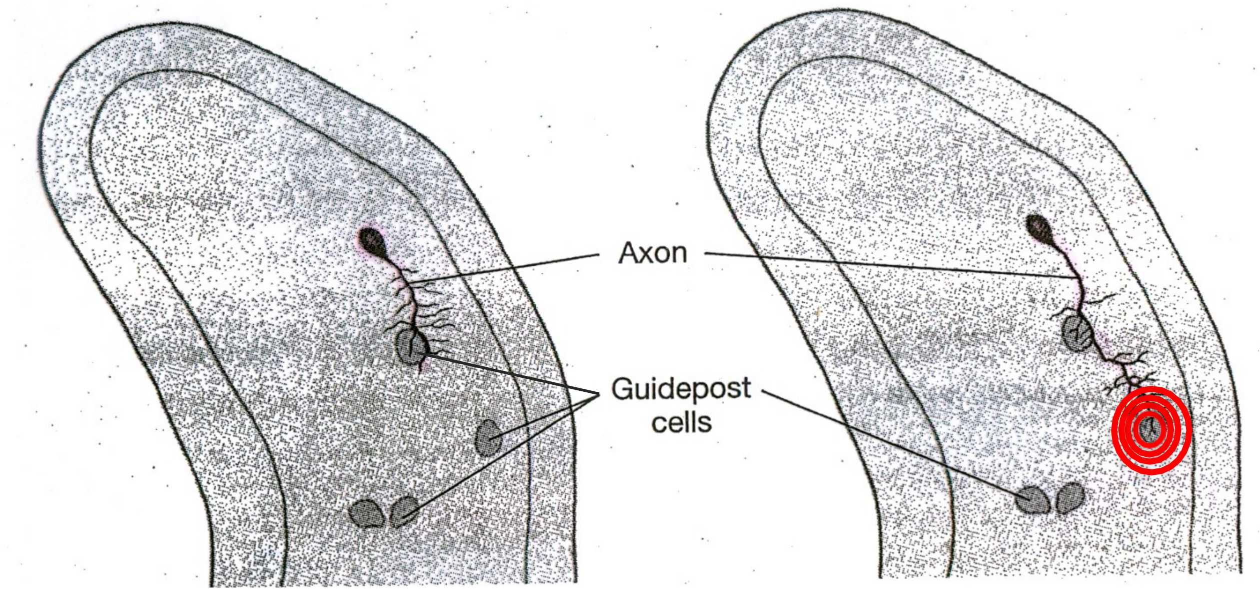
Glia cells, called "**Guidepost Cells**",
ooze neurotrophins that
attract/repel axon Growth Cones



Time 1

Synaptogenesis

Glia cells, called "**Guidepost Cells**",
ooze neurotrophins that
attract/repel axon Growth Cones

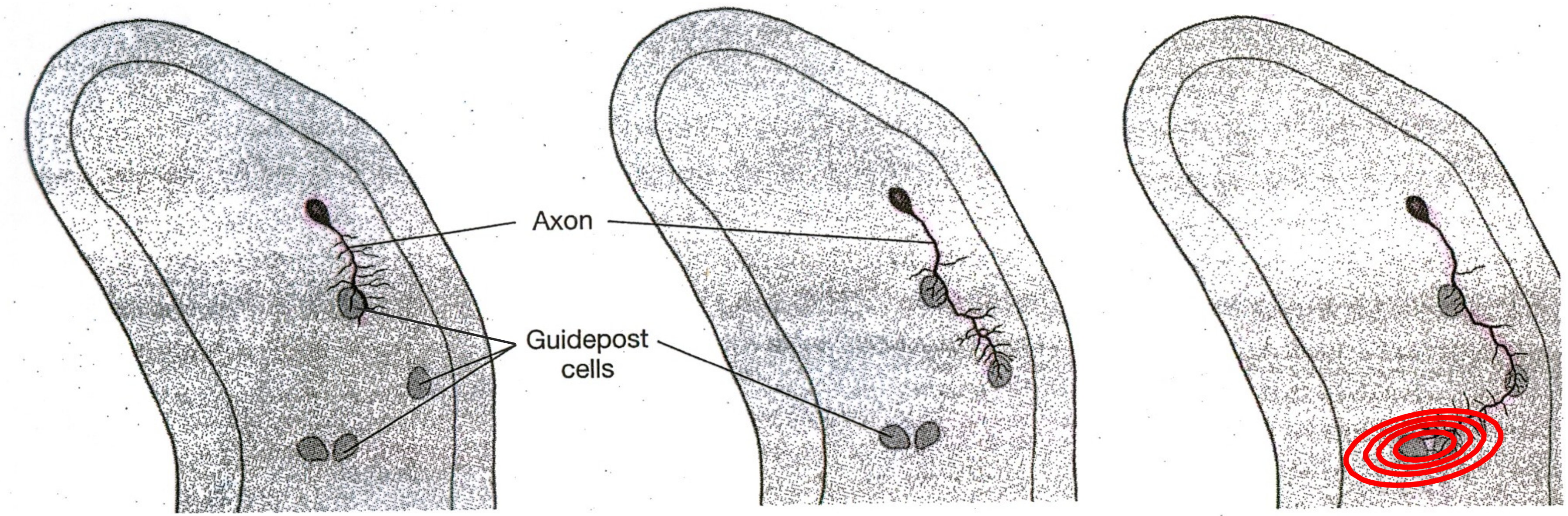


Time 1 Time 2

Slide from Dr. Johnson's COGS17

Synaptogenesis

Glia cells, called "**Guidepost Cells**",
ooze neurotrophins that
attract/repel axon Growth Cones

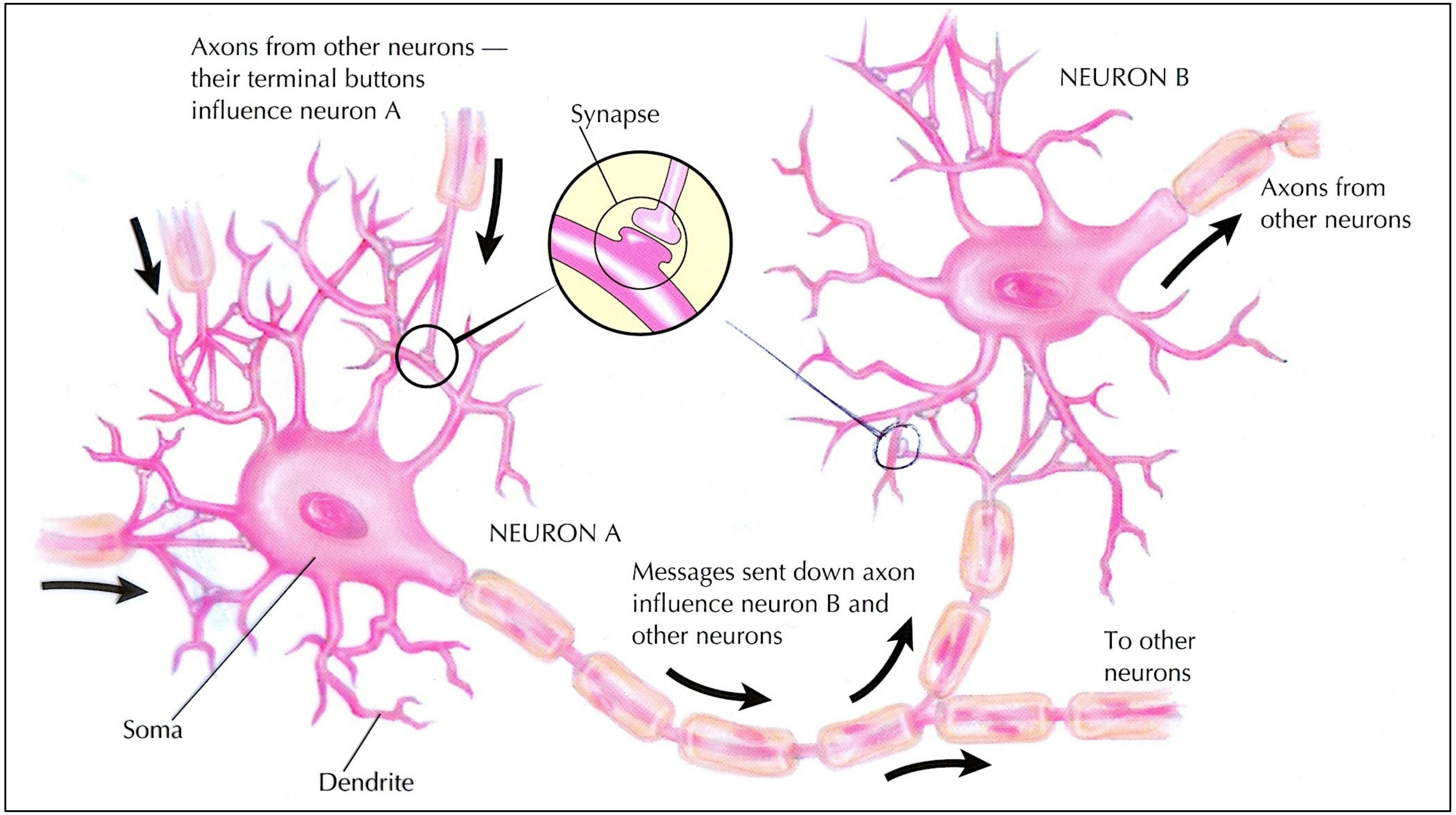


Time 1 Time 2 Time 3

Slide from Dr. Johnson's COGS17

Synaptogenesis

Forming the critical CONNECTIONS between neurons

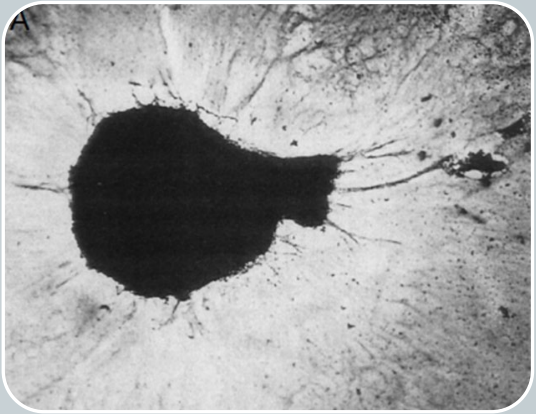


Slide from Dr. Johnson's COGS17

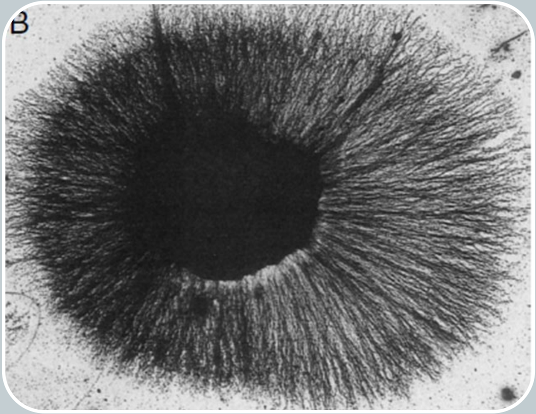
Nerve Growth Factor


ONE HUNDRED YEARS OF RITA

NGF, produced and released by the target tissue, is taken up by the sympathetic axons and transported retrogradely where it acts to promote neuronal survival.



Explanted sensory ganglion in culture without NGF for 24 h.



Experimental sensory ganglion in culture after 24 h NGF treatment.

Rita Levi-Montalcini.

Synaptogenesis

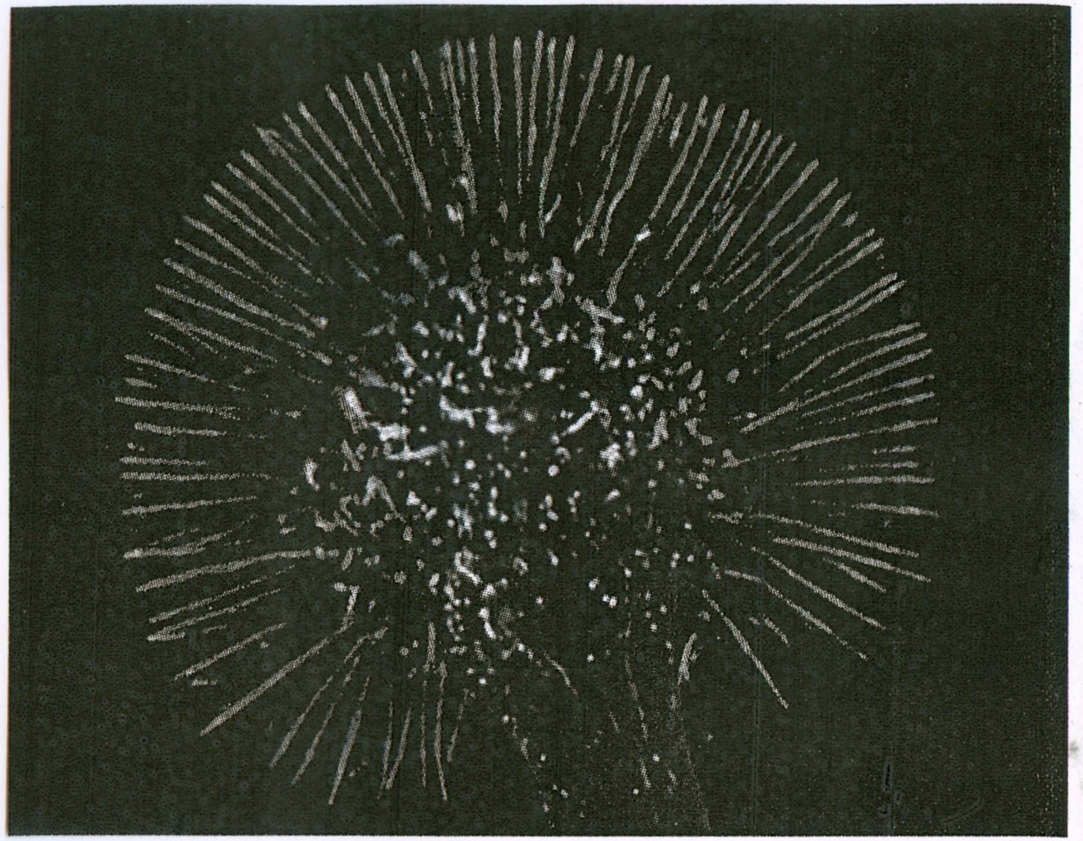


Figure 3.10 The growth cone. This micrograph, a photograph taken by an electron microscope at extremely high magnification, shows the growth cone of a developing neuron with its many filopodia.

At this stage,
the terminal of the axon
is a ciliated

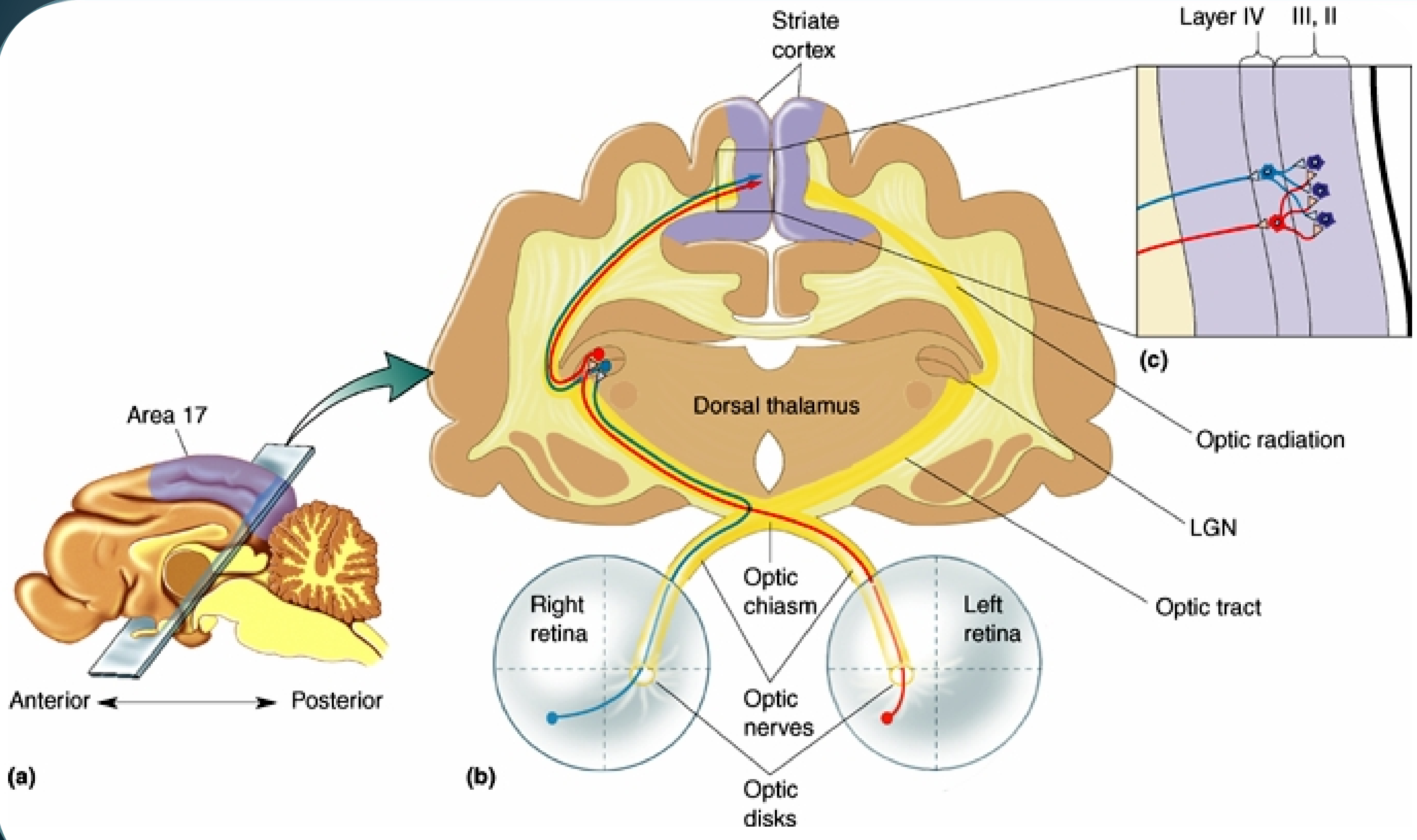
Growth Cone

Its cilia are called

Filopodia

Slide from Dr. Johnson's COGS17

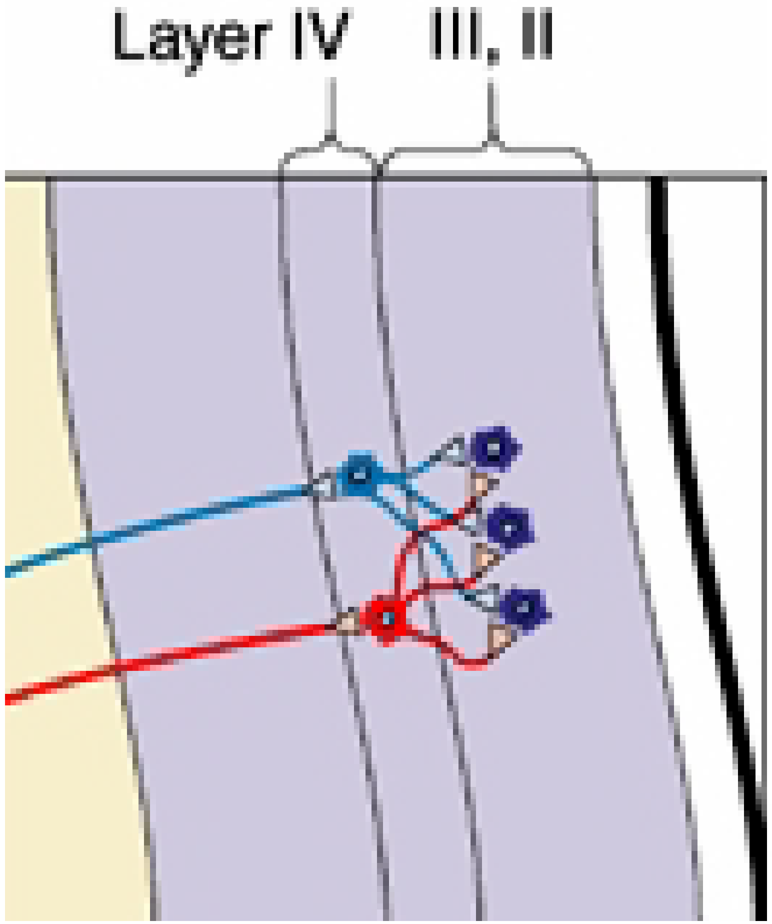
How did it do that?

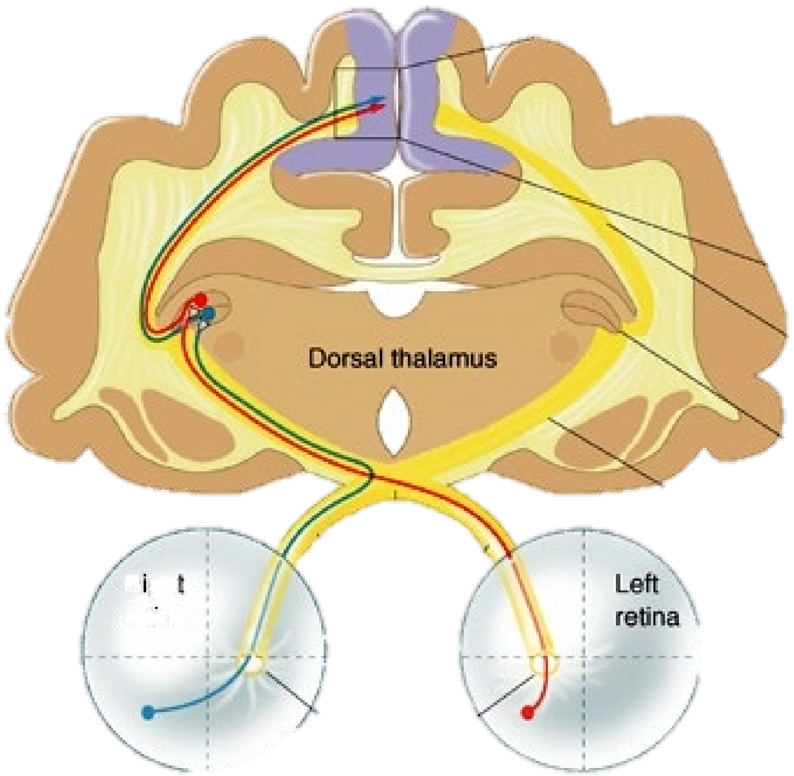


- All RGC extend into optic nerve
- Retina → LGN → V1
- Nasal RGC cross
- LGN – sorted by RGC type, eye of origin, retinotopic position
- LGN→optic radiations→V1
- A17; layer IV; cell type; retinotopic position

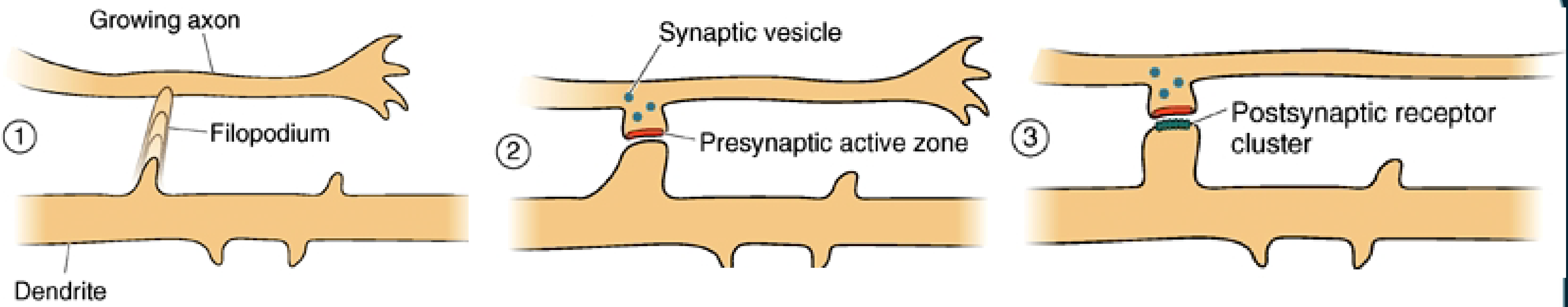
Example: Mammalian retinogeniculocortical pathway

- The site of major convergence of inputs from both eyes is in the projection layer IV cells onto cells of layer III.





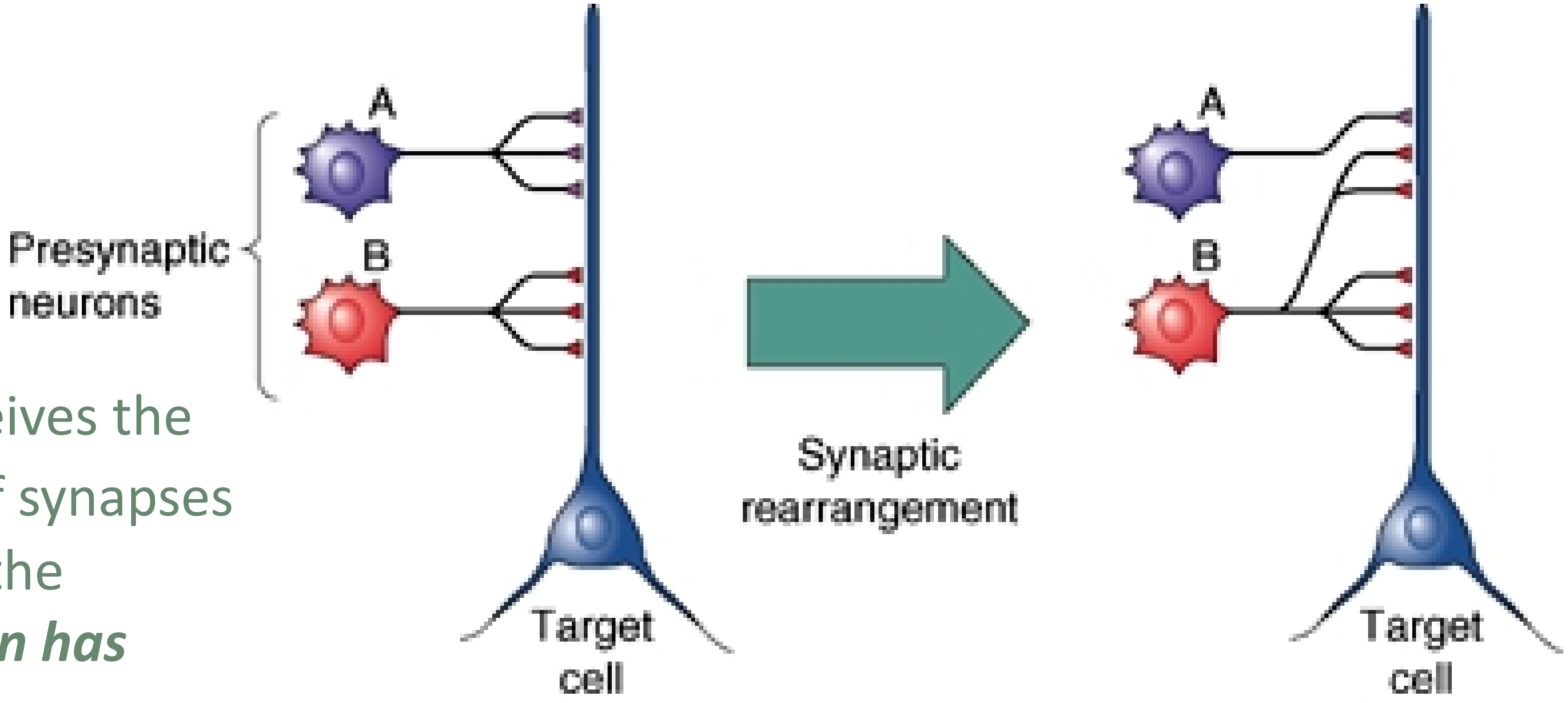
Steps to synapsing in the CNS...



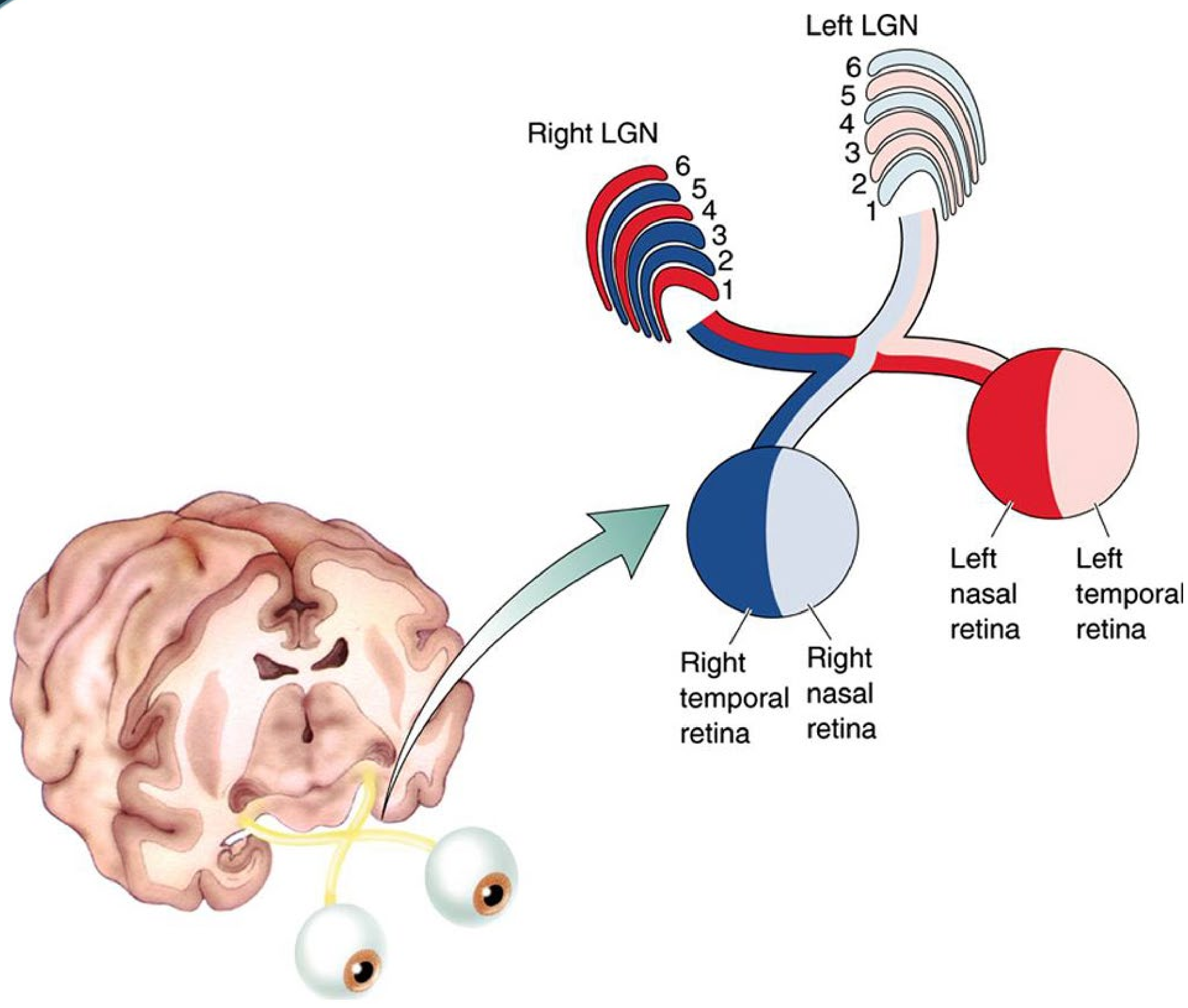
1. Dendritic filopodium reaches out and contacts the passing axon
2. Synaptic vesicles and active zone proteins recruited to presynaptic membrane
3. Receptors accumulate on postsynaptic membrane

...rearrangement...

- Change from one pattern to another
- Consequence of neural activity/synaptic transmission before and after birth
- Critical Period



The target cell receives the **same number** of synapses in both cases, but the ***innervation pattern has changed***.



Retinal ganglion cells send their axons to target neurons in the lateral geniculate nucleus (LGN) in such a way that axons originating from the two eyes terminate in adjacent but non-overlapping eye-specific layers.

...segregation...Refinement of synaptic connections

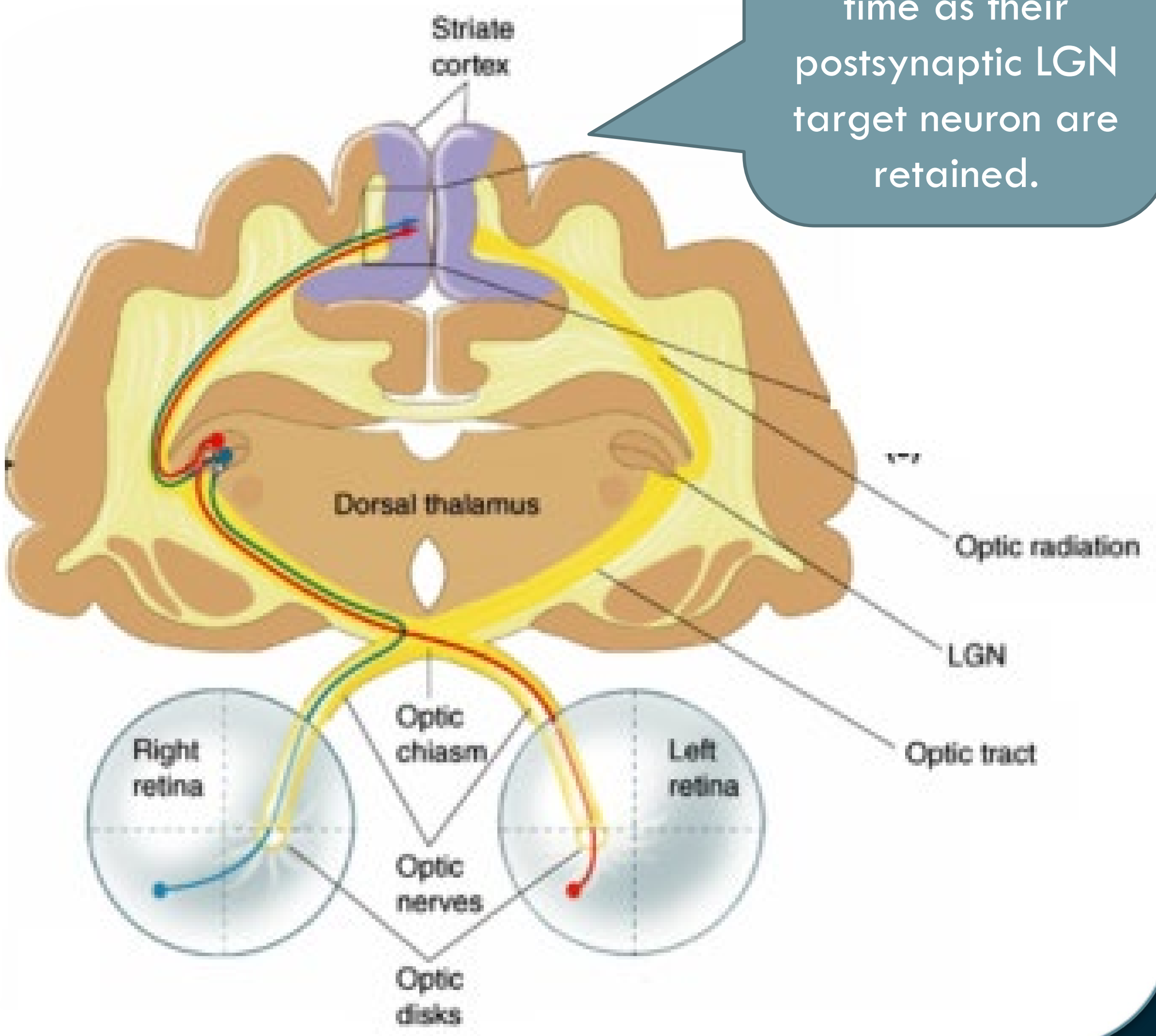
Only retinal terminals that are active at the same time as their postsynaptic LGN target neuron are retained.

Silencing retinal activity with TTX prevents this process of segregation –

Contralateral RGC axons 1st to reach LGN → they spread out over the ENTIRE area

Later, ipsilateral projection arrive and **intermingles** with axons of contralateral eye.

Axons from both eyes **segregate** into eye-specific domains.



How can the firing of retinal ganglion cells give rise to a segregated pattern of eye input within the LGN?

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 602–608, January 1996
Colloquium Paper

This paper was presented at a colloquium entitled "Vision: From Photon to Perception," organized by John Dowling, Lubert Stryer (chair), and Torsten Wiesel, held May 20–22, 1995, at the National Academy of Sciences in Irvine, CA.

Emergence of order in visual system development

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Shatz, C.J. (1996) PNAS Vol. 93, pp. 602-608

"Cells that fire together wire together."

1. Random action potentials are not sufficient to segregate the retinal axon projections in the LGN.

2. Precise temporal and spatial patterning of neural activity is required for segregation --

3. If the axons from both eyes are stimulated synchronously – segregation is prevented (same results as with TTX)

4. However, if the two nerves are stimulated asynchronously, then segregation proceeds.

Shatz, C.J. (1996) PNAS Vol. 93, pp. 602-608