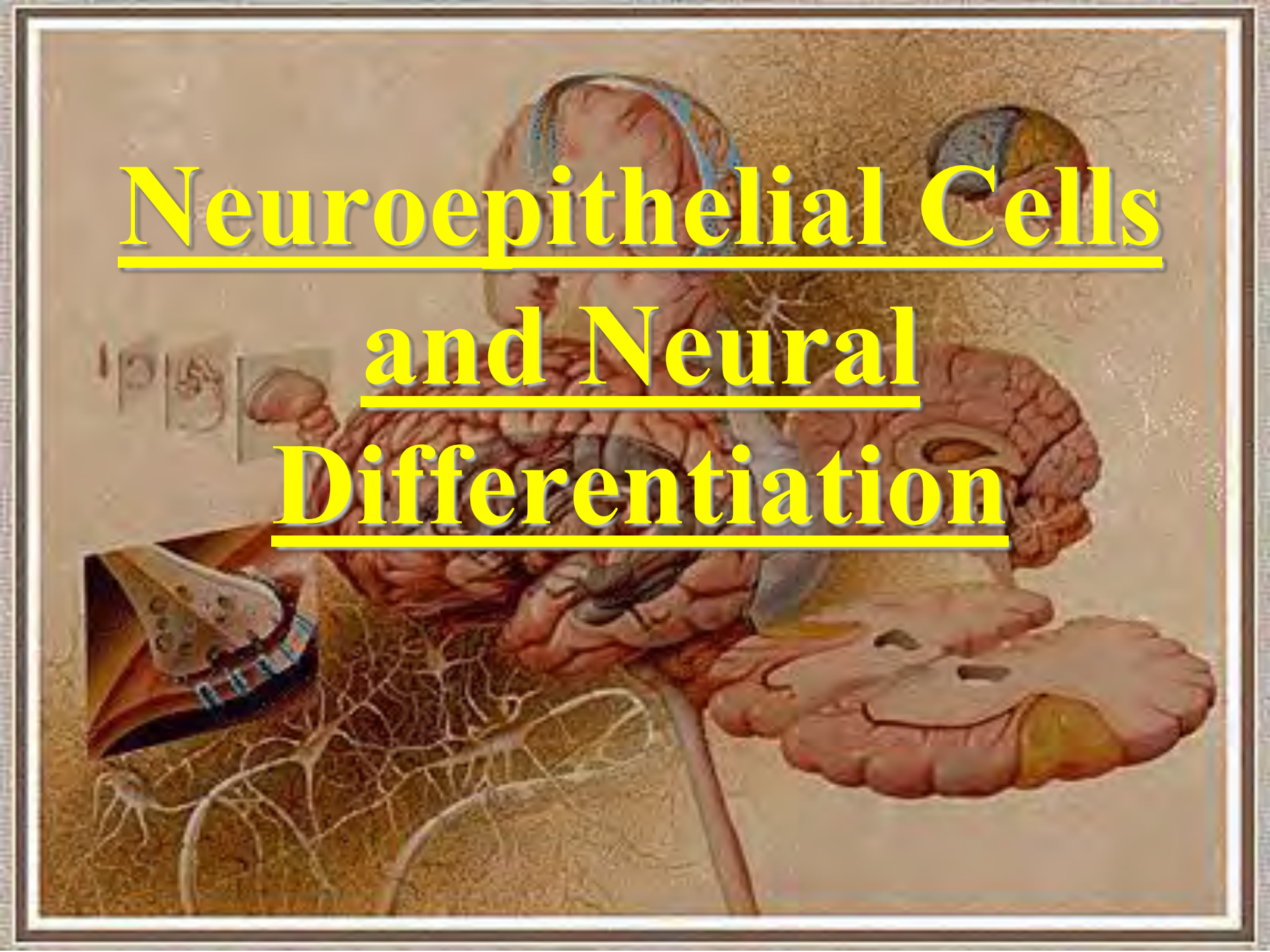
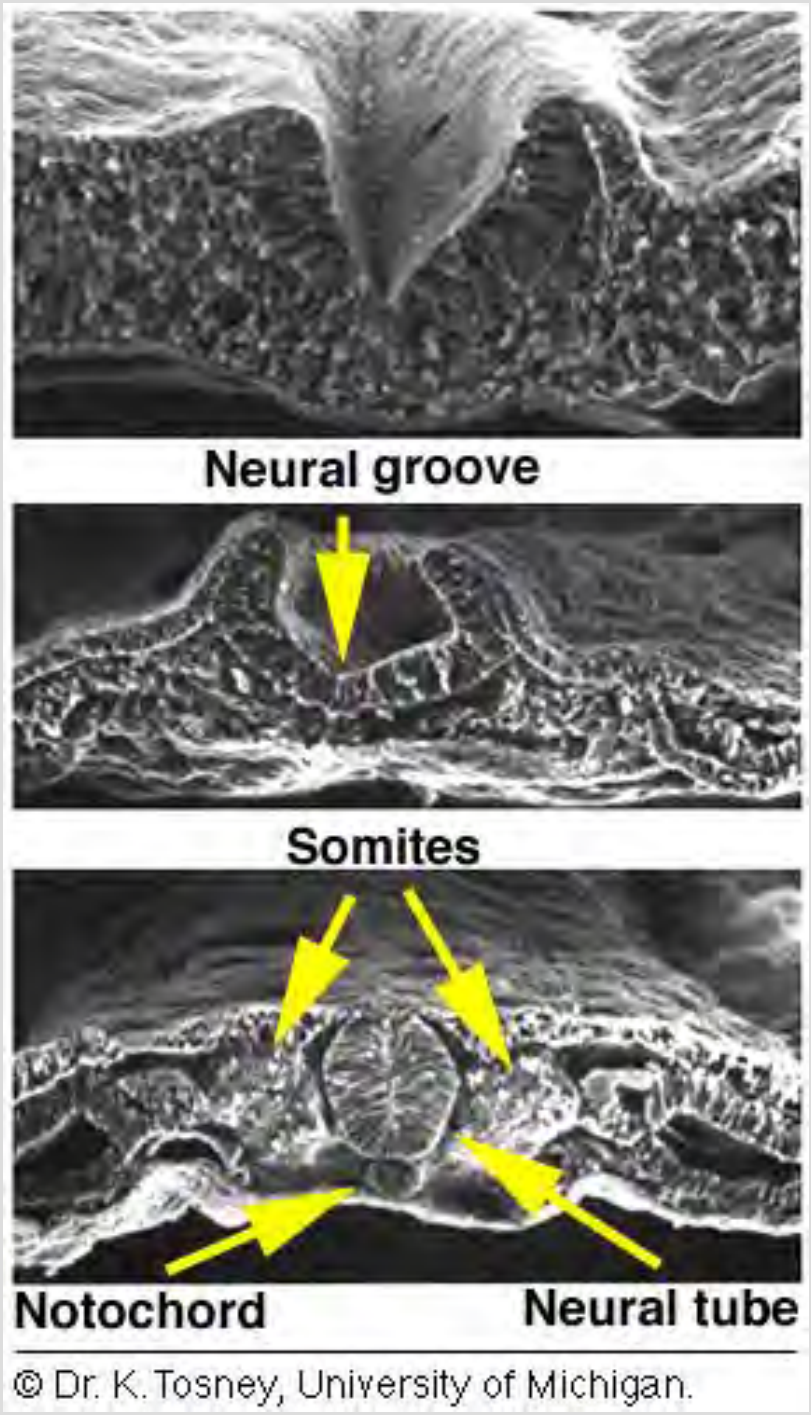
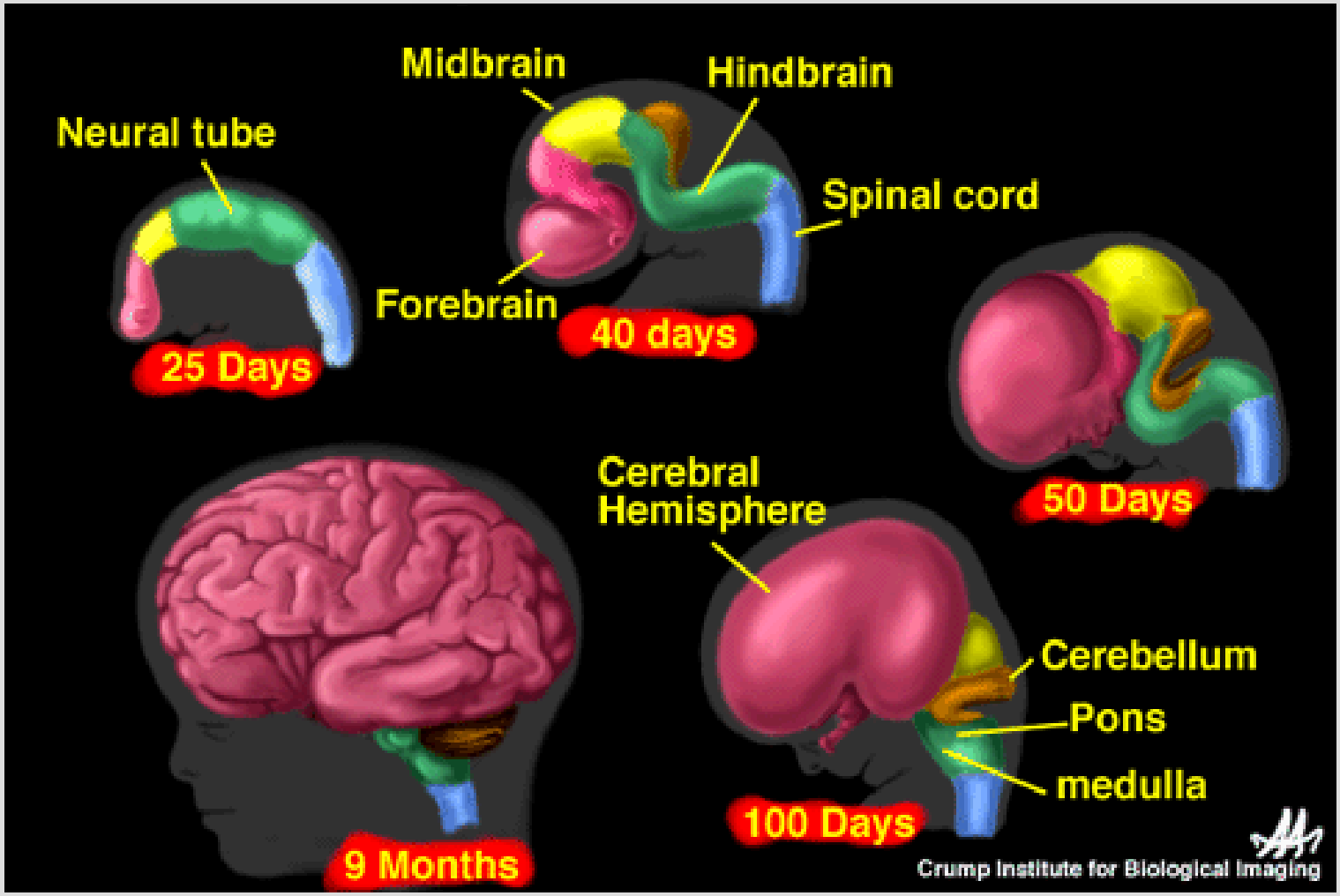

Neuroepithelial Cells
and Neural
Differentiation

Neurulation



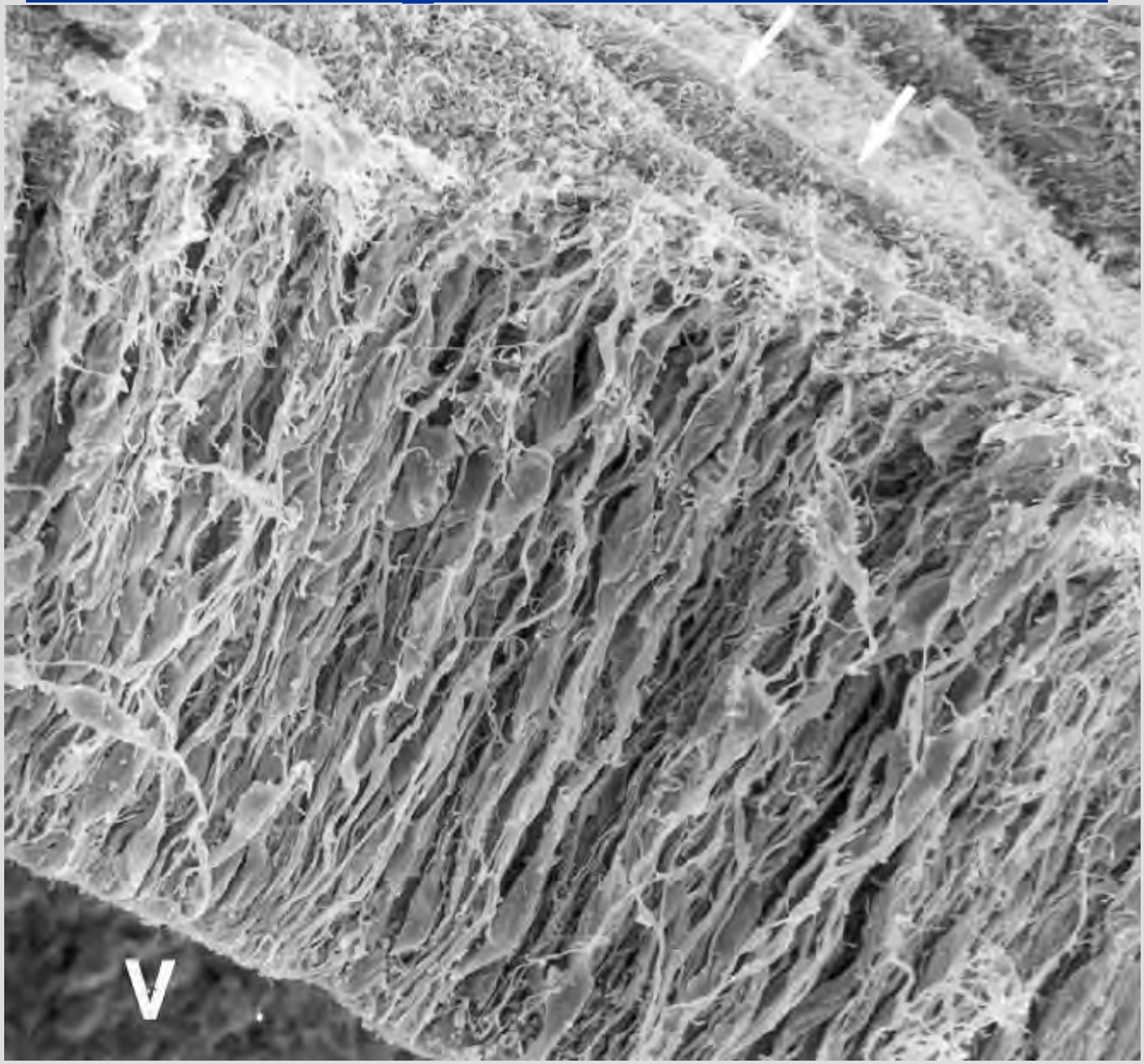
- The cells of the neural tube are **NEUROEPITHELIAL CELLS**
- **Neural crest cells** migrate out of neural tube
- Neuroepithelial cells are embryonic stem cells of the brain
- Will give rise to 100 billion neurons and ~5x glial cells
- Neuroepithelial cells have:
- An unusual cell cycle
- An unusual cell division



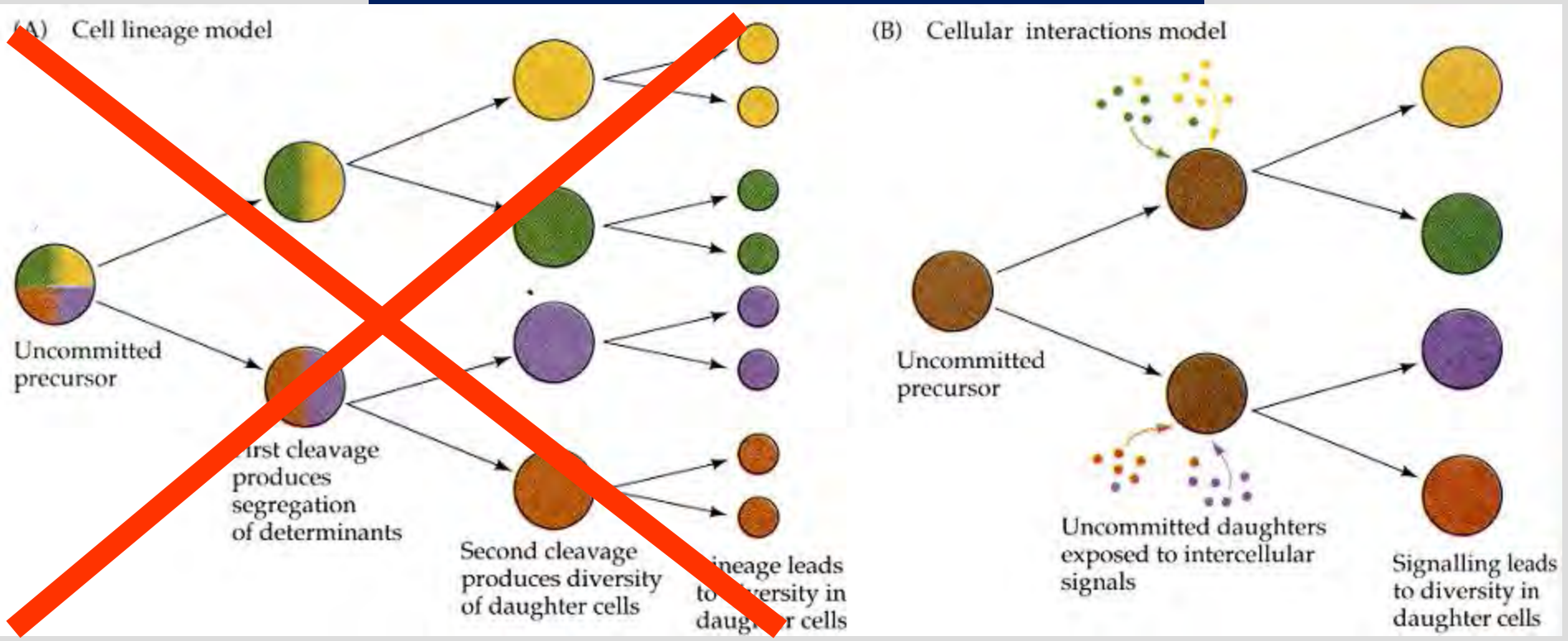
- Already very early – before the differentiation of the first nerve cells in the neural tube, a local specialization of brain regions can be detected.
- Segmentation or regionalization – the neural tube is not identical along its length

Neuroepithelial Cells: Unusual Precursor Cells of the Embryonic Brain

Neuroepithelial Cells



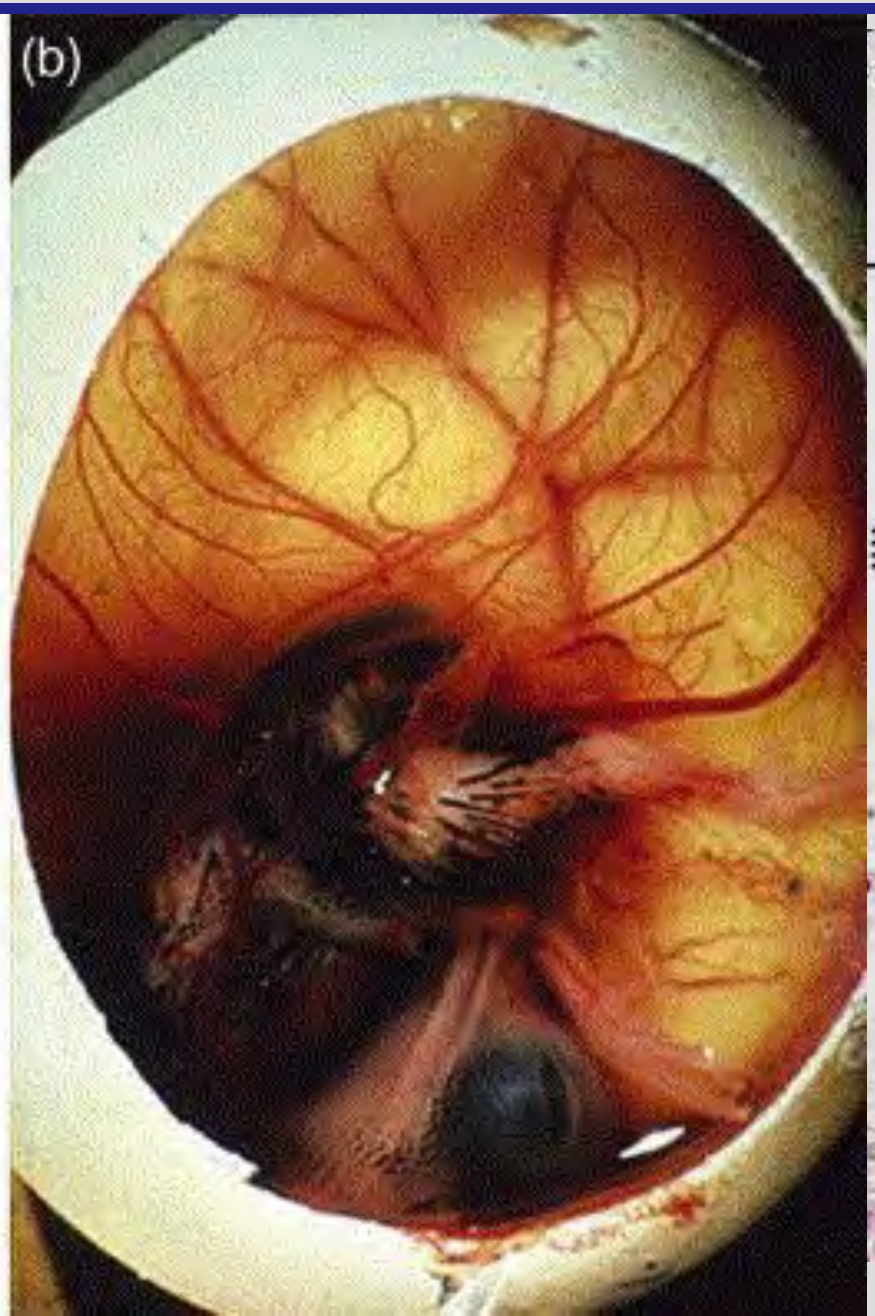
What Kind of Precursor Cells are Neuroepithelial Cells?

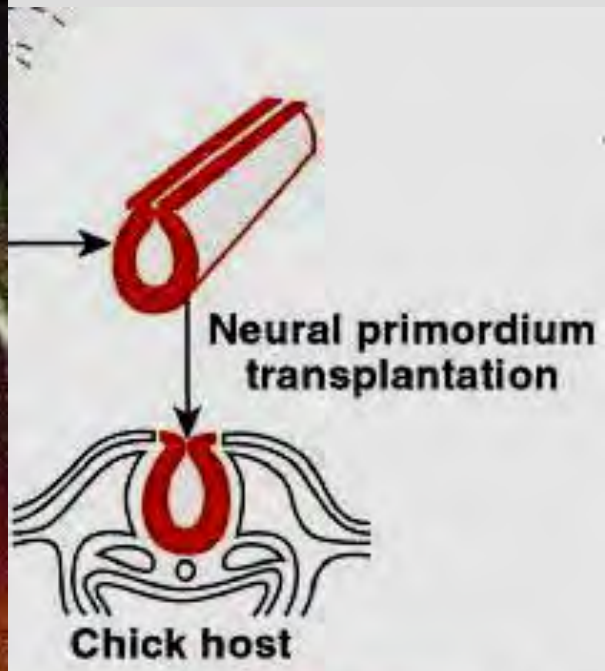


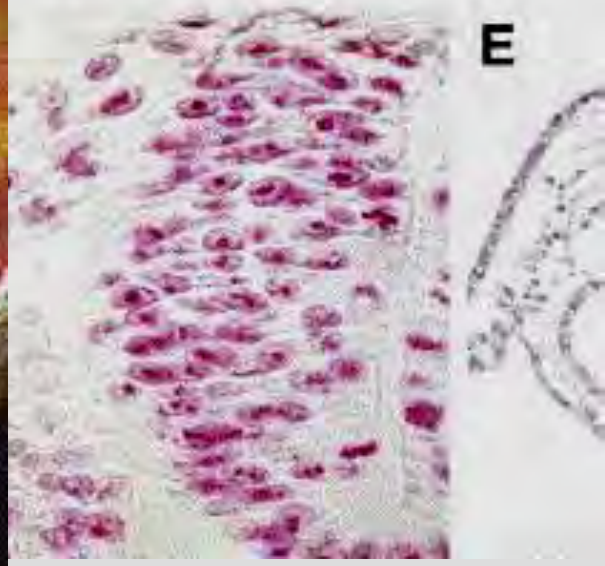
- intrinsic genetic signals; **European model**; do what your history tells you
- differentiate according to signals from their environment; **American model**; do what your neighbors tell you
- Experimental evidence in vertebrates suggests American model to be correct initially, whereas a combination of both models is correct at later stages – evidence: transplantation, labeling

Chick-Quail Chimera to Study Lineage

- Introduced
  Le Dourain
- Quail cells
  nucleolus F





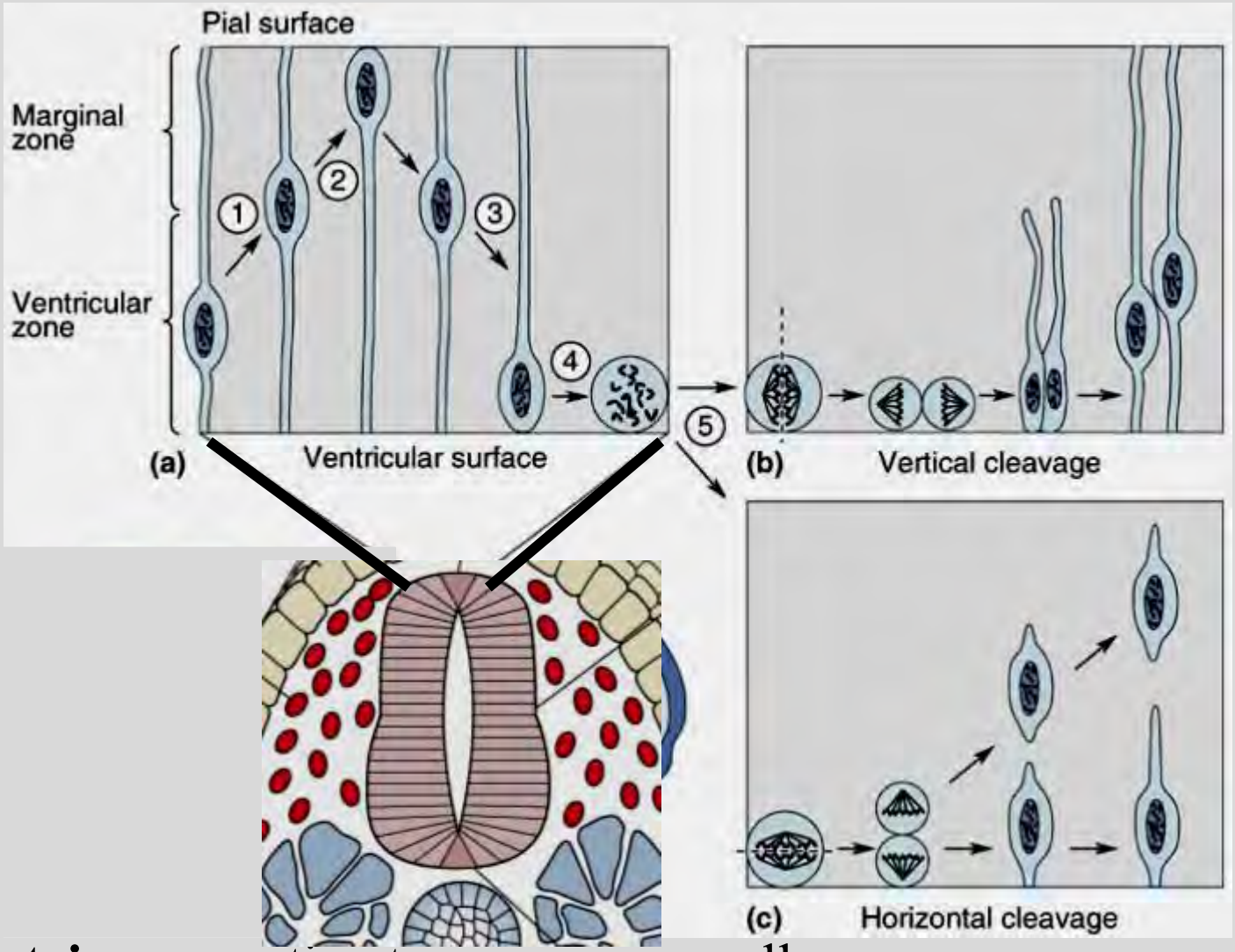


Chick-Quail Chimera

- How does one know that the transplantation has worked?
- Let the chicken hatch and analyze the pigmentation
- Pigment cells are derived from neural crest cells

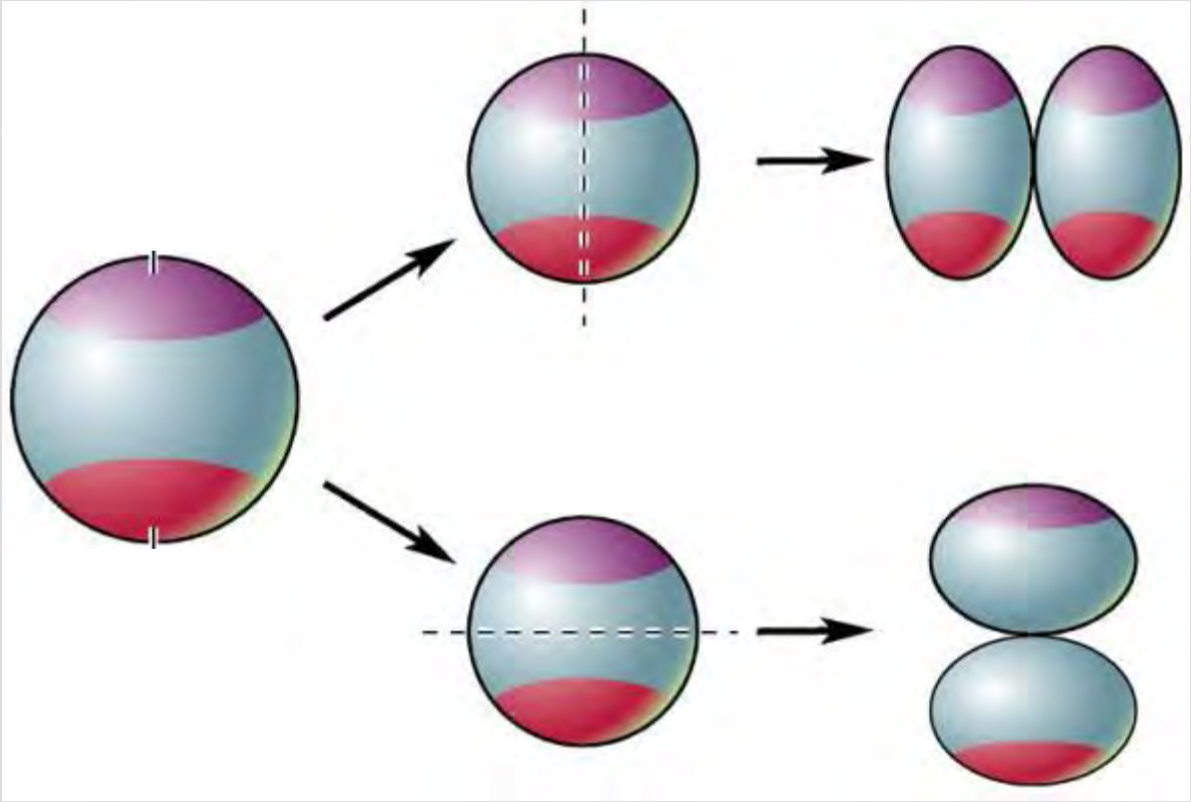
How do Neuroepithelial Precursor Cells Differentiate into Neurons?

Two Types of Cell Divisions of NE Cells



- **Symmetric**: generating two precursor cells
- **Asymmetric**: generating one precursor cell and one postmitotic neuron

Inheritance of Cell Constituents After Horizontal or Vertical Cleavage

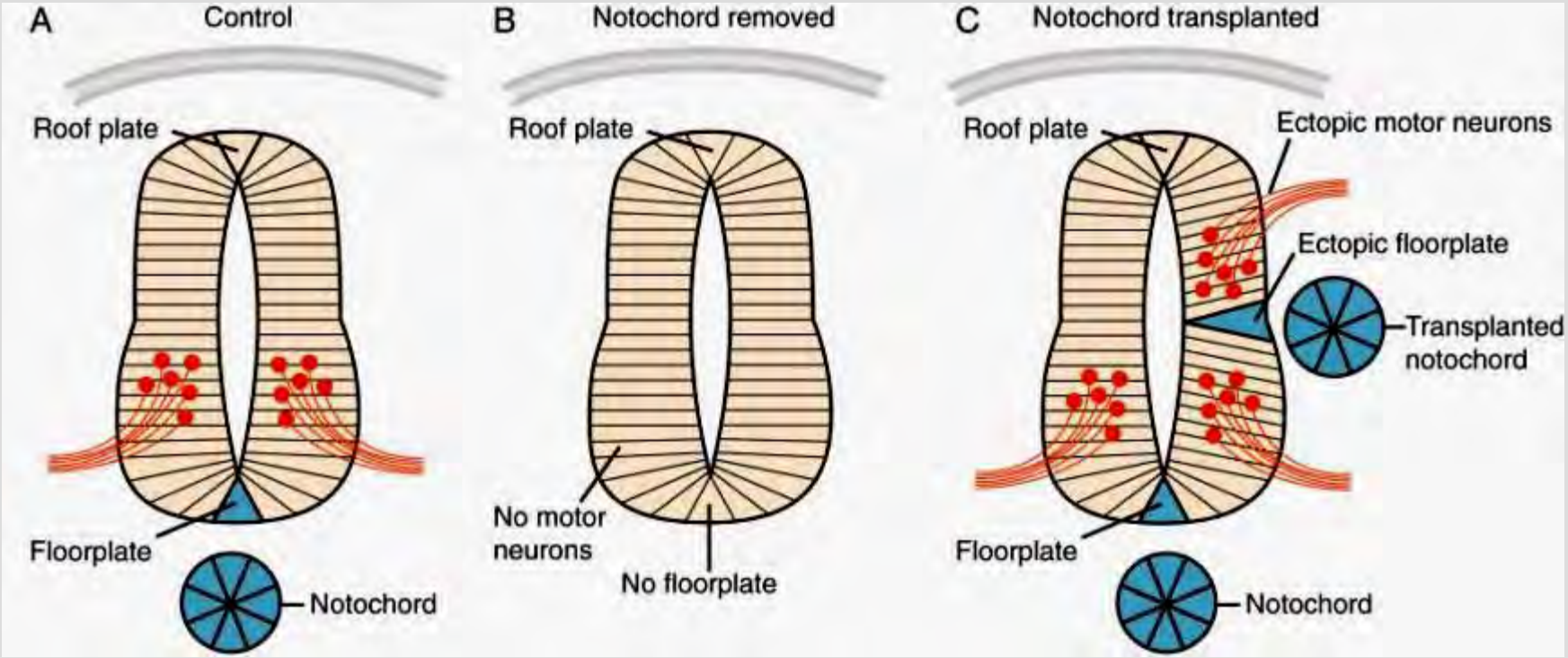


- Asymmetric cleavage generates a neuron which migrates away towards the basal pole and a precursor cell which remains at the ventricular border
- Neuronal fate induced by expression of **PRONEURAL** genes
- Notch inhibits proneural gene expression and, thus, maintains progenitor cell fate
- If cell inherits notch, it will be maintained in a precursor state

Neurogenesis: What are the Molecular Mechanisms that Induce Neuroepithelial Precursor Cells to Become Neurons?

- Let's look at the spinal cord

The Notochord is Necessary and Sufficient for D – V Axis Formation

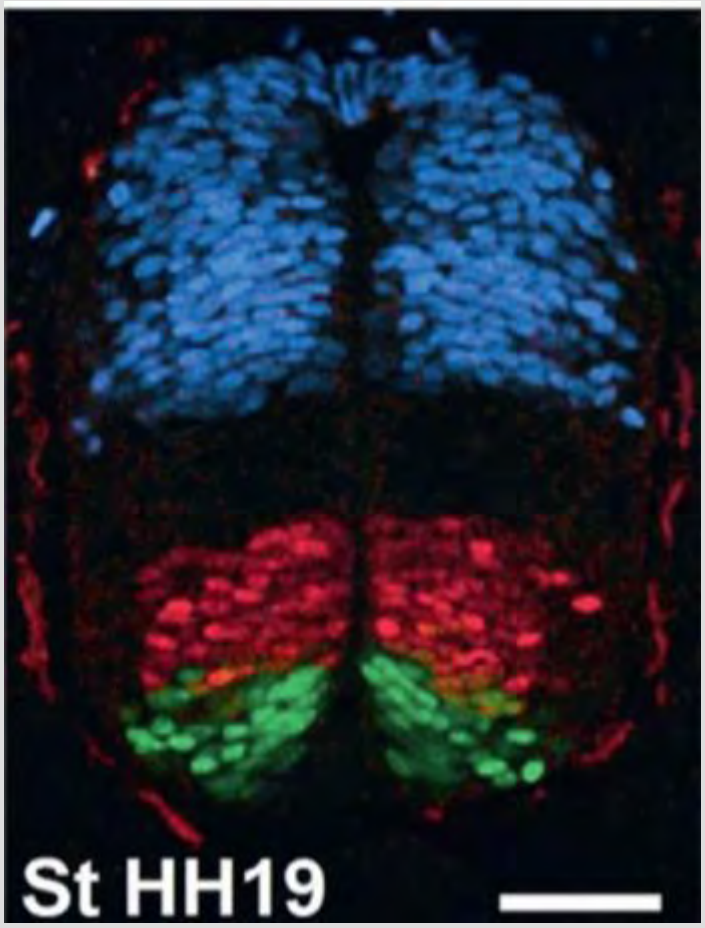


- Transplantation experiments done originally by Johannes Holtfreter (1934) and redone by M. Plascek and T. Jessell
- Notochord specifies floor plate and cells from the floor plate specify motoneurons
- What are the molecules responsible for this effect?

Sonic the Hedgehog

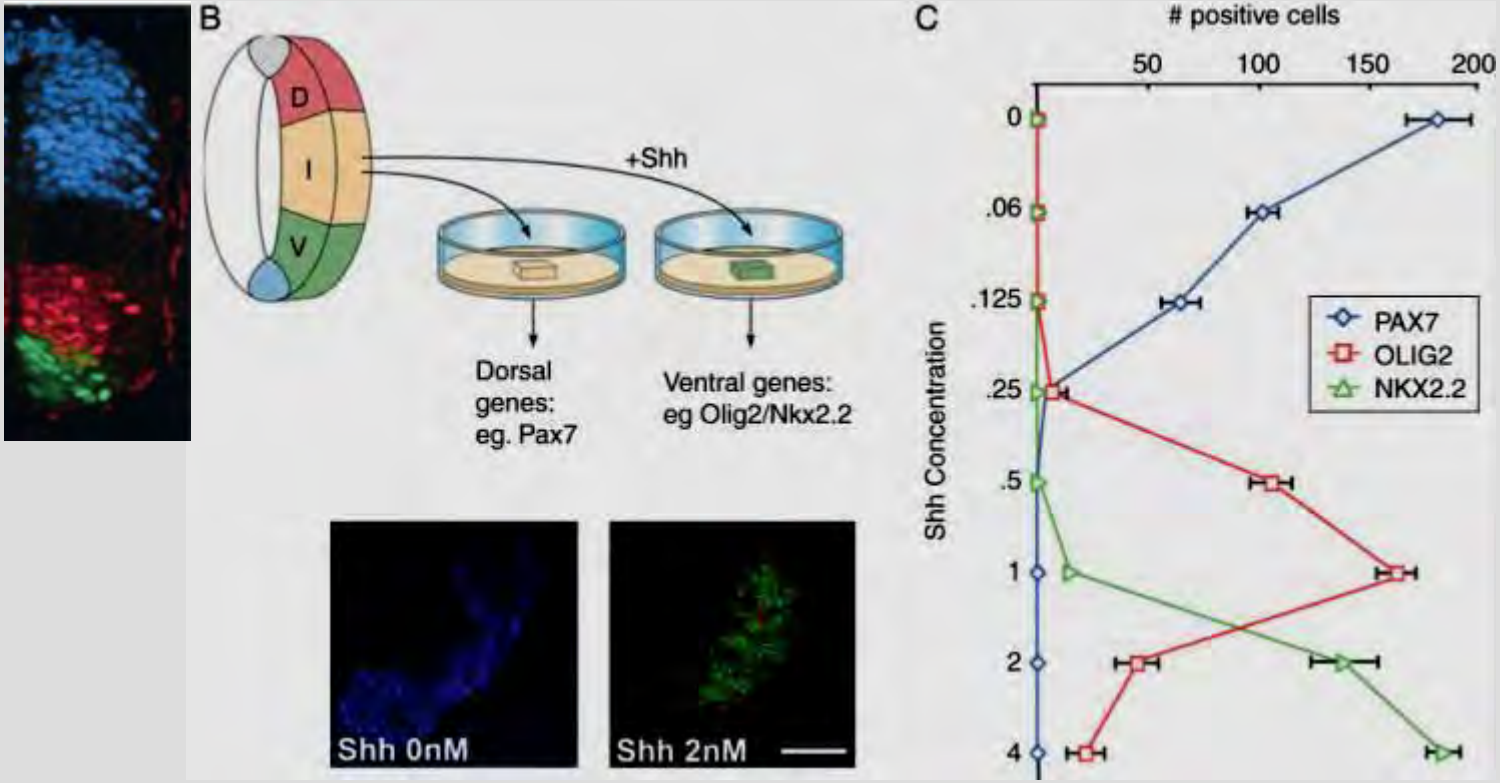
- Favorite cartoon figure of Clifford Tabin (Harvard) who discovered (with others) this gene

Transcription Factors Define Domains within Neural Tube



- 3 genes define particular domains along D – V axis of neural tube
- Dorsal: Pax7 (blue); intermediate Olig2 (red); ventral: Nkx2.2 (green)
- Genes are useful markers for positional information along D – V axis
- Secreted protein expressed by notochord and floor plate: SHH

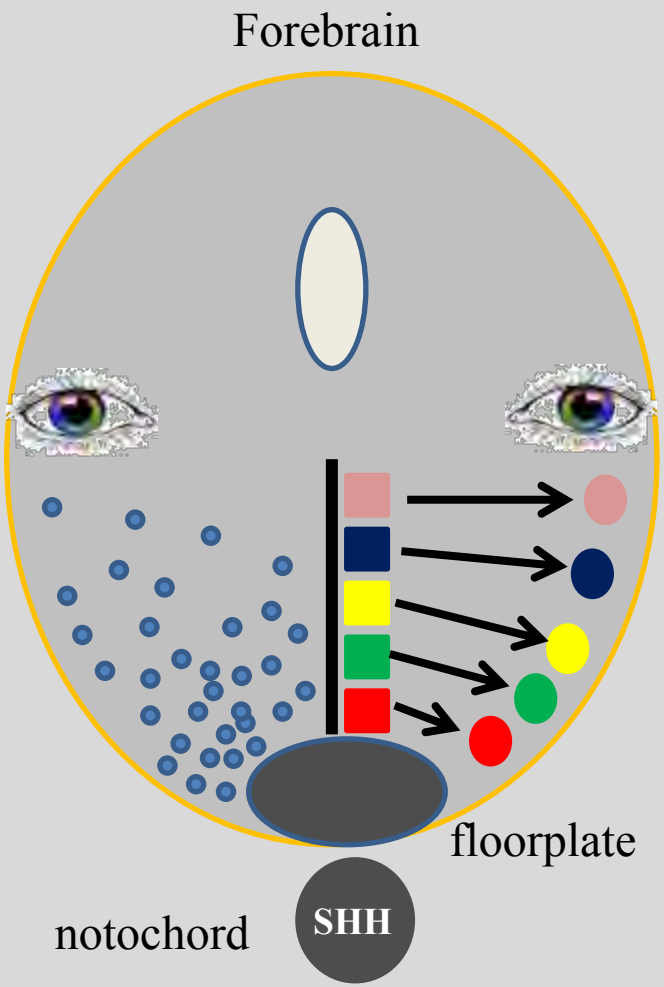
Induction of D – V Axis by SHH



Modified from Dessaud et al., 2008

- SHH added to neural tube explant induces floor plate, expression of genes and differentiation of neurons in a dose-dependent manner (gradient is formed in neural tube)
- Activity-blocking antibodies inhibit D-V axis formation, mice with targeted deletion of SHH form no D-V axis
- SHH ventralizes neural tube by being a morphogen

Neural Identity in the Spinal Cord Depends on Sonic Hedgehog Concentration

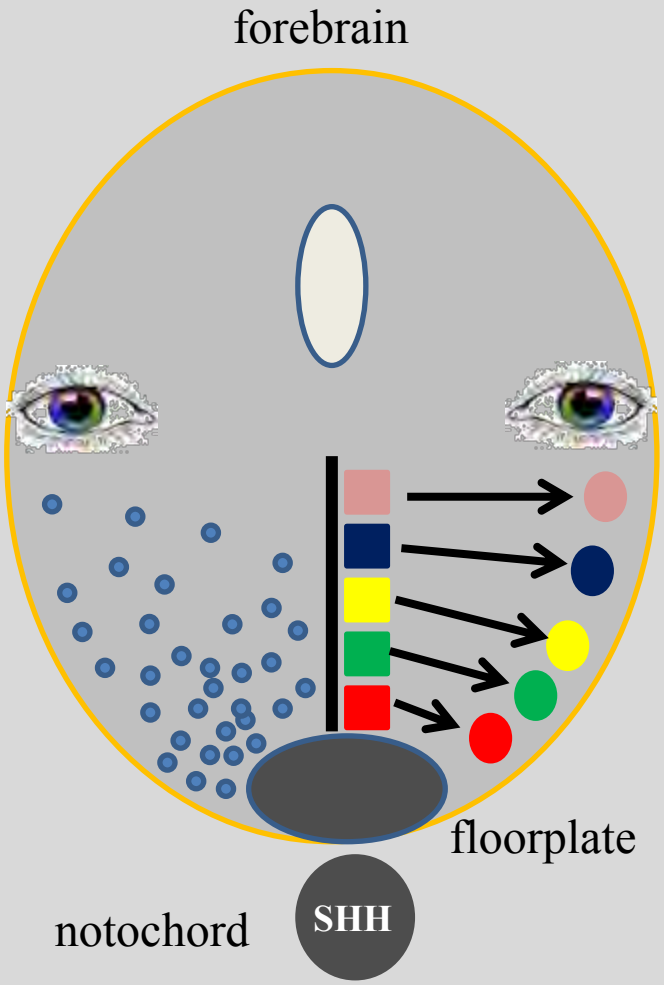


- Hypothesis: a gradient of SHH signaling controls the fate of the neurons in the CNS and spinal cord
- How can one test this hypothesis??
- How can a single molecule induce all these different neurons??
- Formation of gradient (2-3 fold difference)

What happens if you systematically reduce SHH concentration in the neural tube?

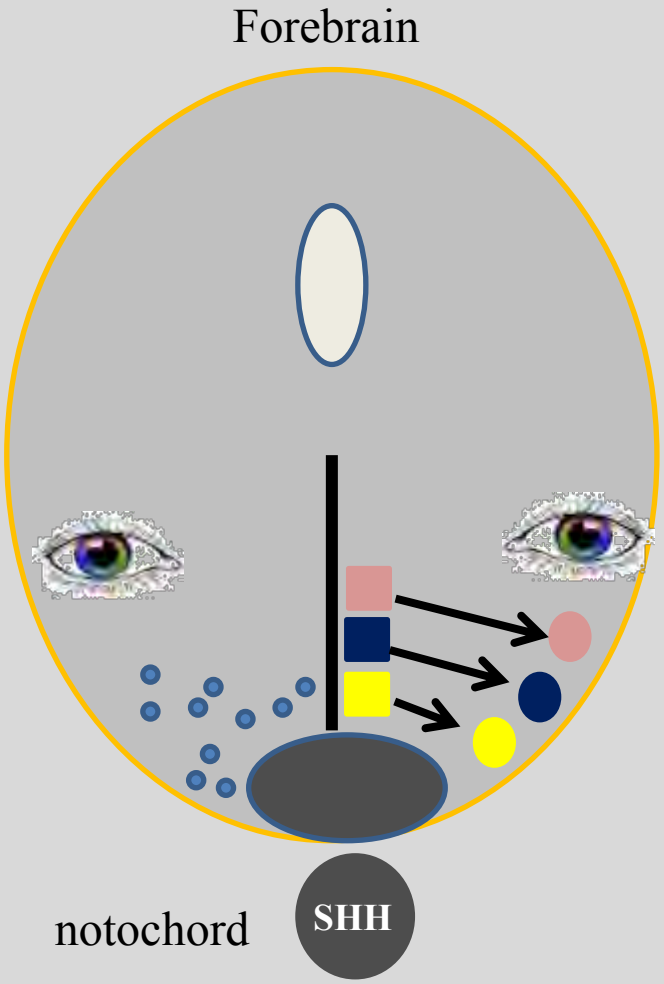
- Hypothesis: differential survival of spinal cord neurons

Neural Identity in the Spinal Cord Depends on Sonic Hedgehog Concentration



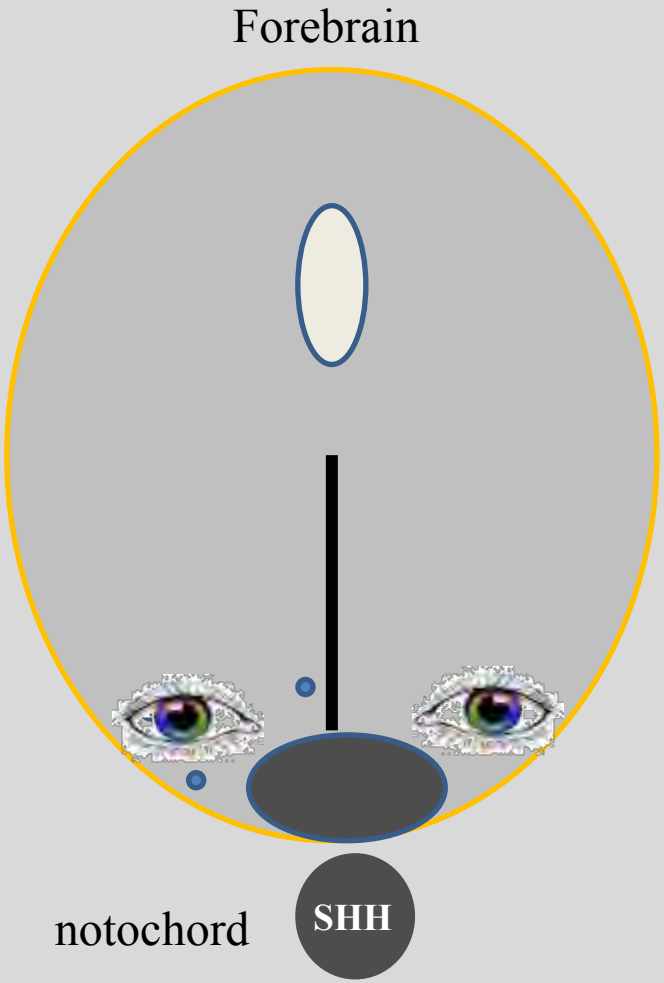
- The first cells that get lost are those that require a high SHH concentration

Neural Identity in the Spinal Cord Depends on Sonic Hedgehog Concentration



- Reduced amount of SHH allows the survival only of those neurons that under physiological conditions differentiate in the presence of low amounts of SHH

Neural Identity in the Spinal Cord Depends on Sonic Hedgehog Concentration

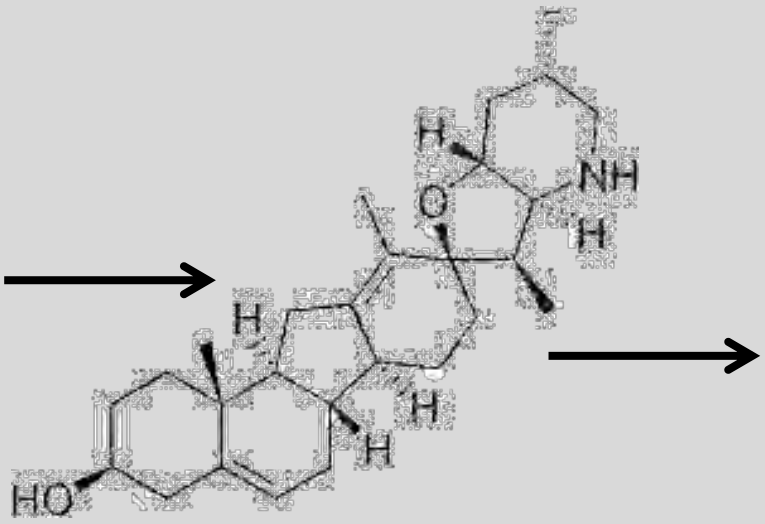


- In the case of the elimination extreme: all except the most dorsally located neurons would get lost - only eye fields

Hedgehog Signalling Failure: Cyclopia

False hellebore – eaten by herbivores like cattle or sheep

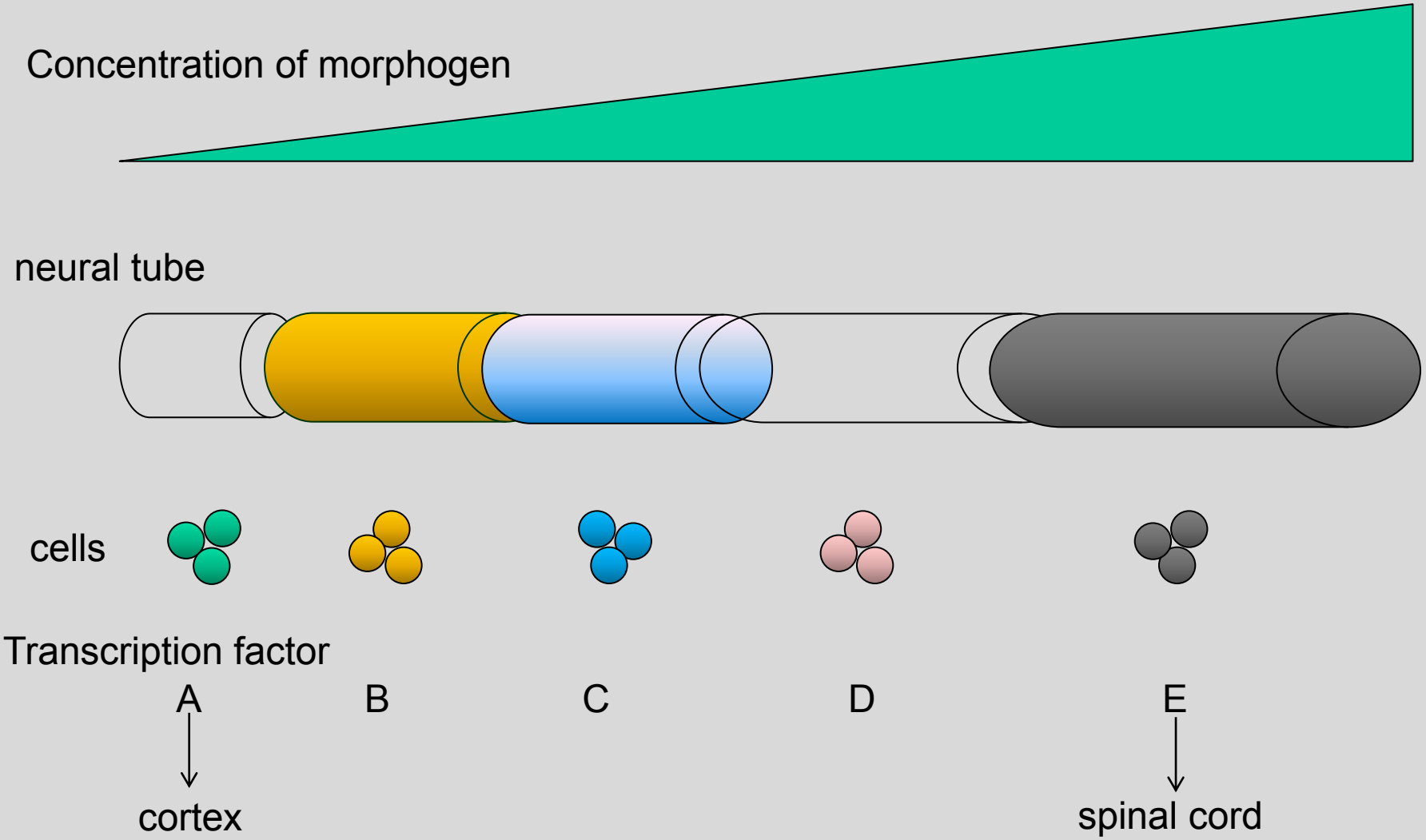
cyclopamin blocks SHH signaling through its receptor



Newborn lambs or calves develop cyclopia – single eye plus many other nervous system defects

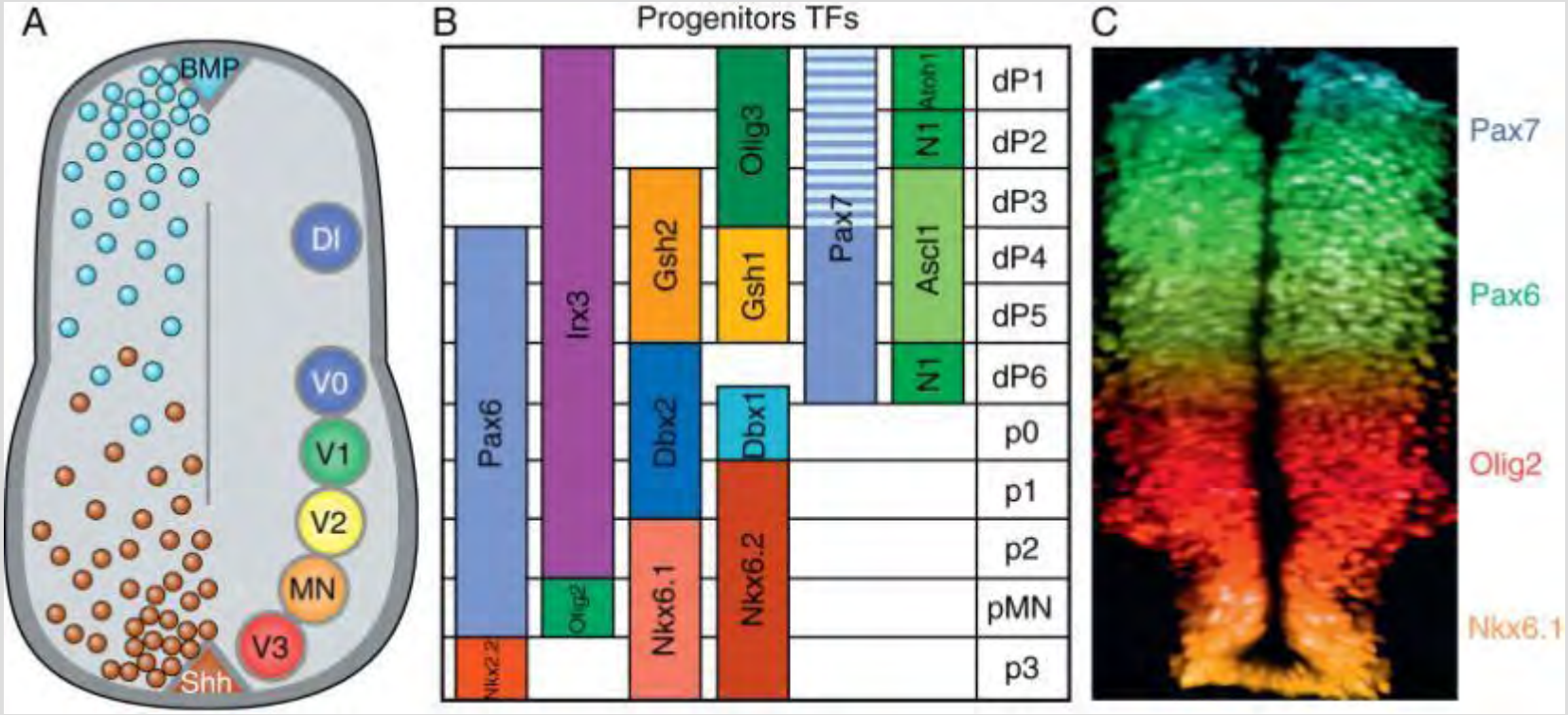
In humans and mice: cyclopia after mutations in genes involved in SHH signaling

How Cells Convert Positional Information into Cellular Identity



- Primary transcription factors will induce secondary

Primary Transcription Factors



- In addition to the "ventralizing" morphogen SHH, BMP is a "dorsolizing" morphogen – antagonizing signals sharpen boundary
- Different neuronal identities are generated by sequential activation of a mosaic of transcription factors due to different concentrations of morphogens
- This shows that complexity is generated by a sequence of simple signals
- An initially uniform cell population due to a grades signal and a sequential activation of transcription factors produces neurons with different identities