Chapter 3

Genesis and Migration

Functional homologies between neurogenic genes:
Neurogenic gene sog (~chordin) inhibits dpp (~BMP) signaling

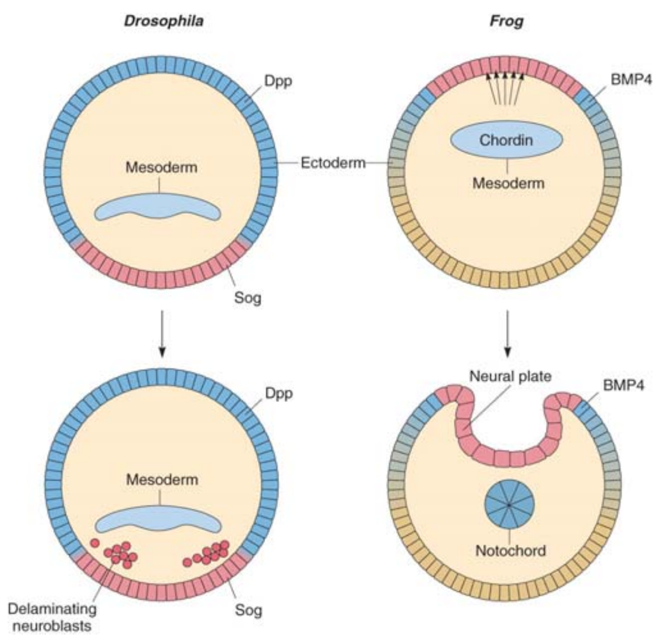


Fig. 1.19

Proneural genes experience Notch-Delta Lateral Inhibition

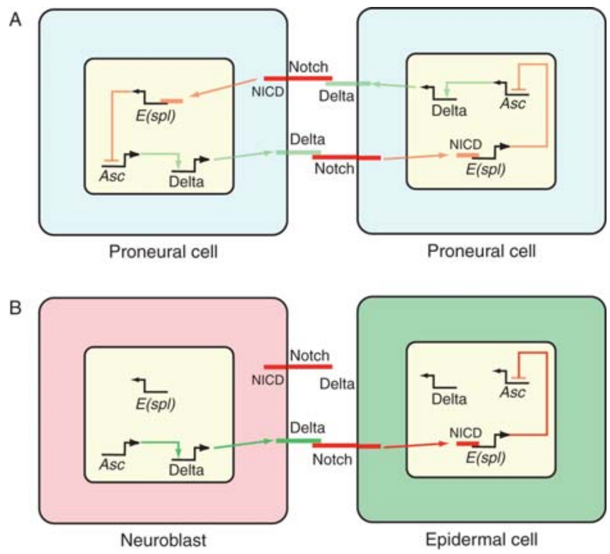
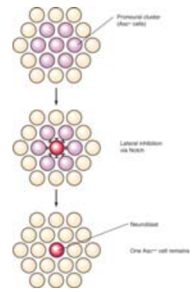
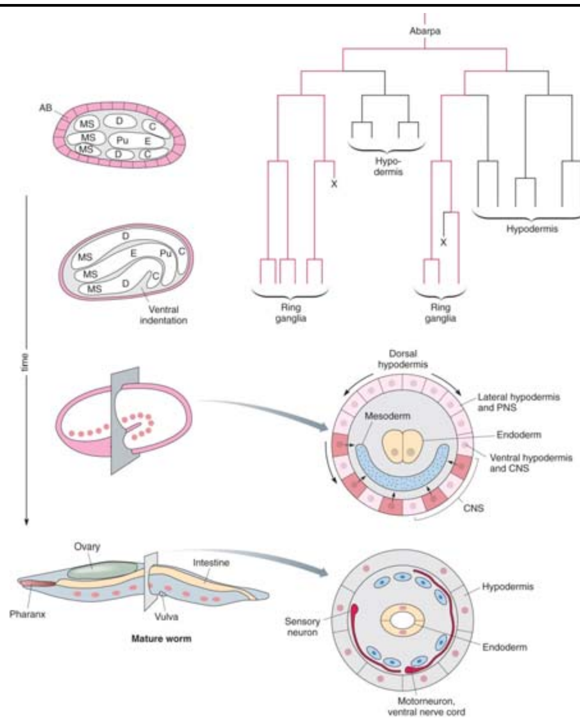


Fig. 1.28



Notch/Delta interaction blocks neural fate in neighboring cells by blocking Asc via Hes.

Fig. 1.29



C. elegans
- •Constant cell number (eutely)
- •Lineage-dependent

Fig. 1.3

Drosophila:
•Stereotyped pattern of neurogenesis
•Lineage-dependent

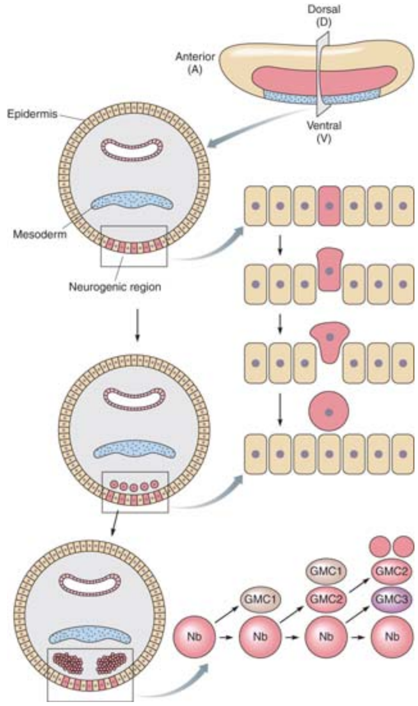
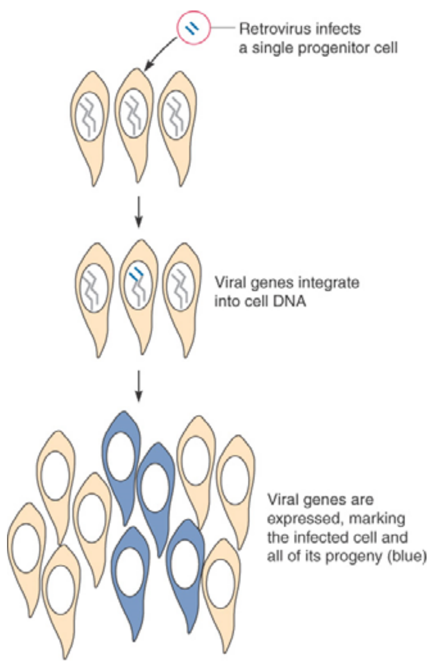


Fig 1.5

Retroviral labeling technique



Proliferation in a pseudostratified epithelium

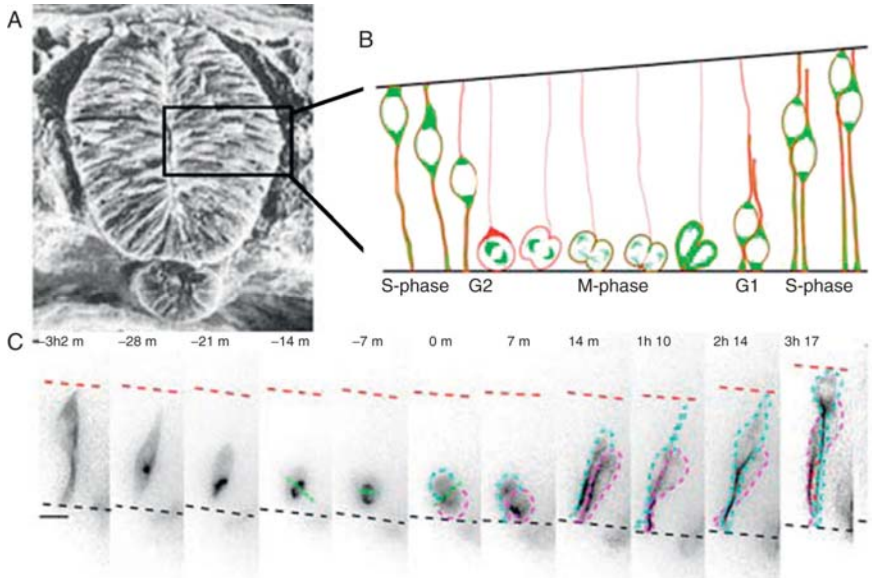


Fig 3.1

Vertebrates:
- •Fate and position are less predictable
- •Clonal analysis reveals indeterminate fates of daughter cells

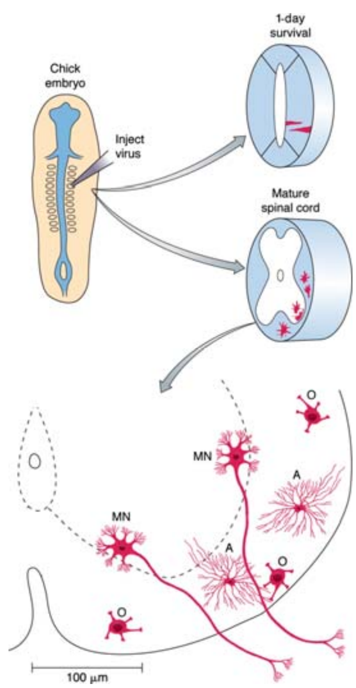
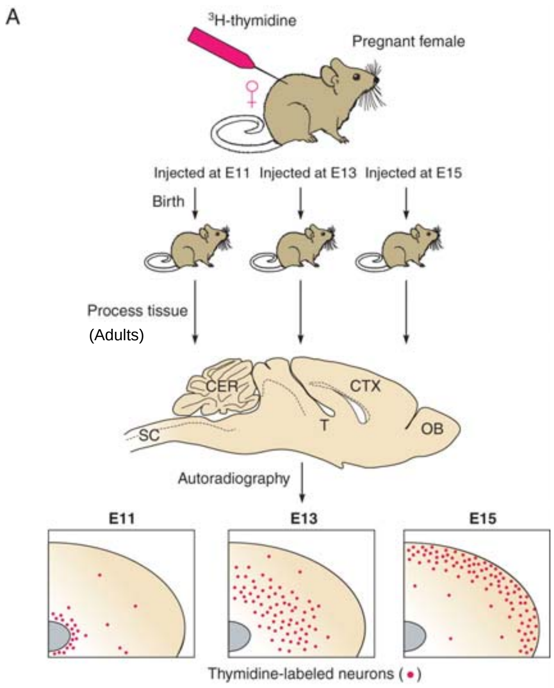


Fig 3.2

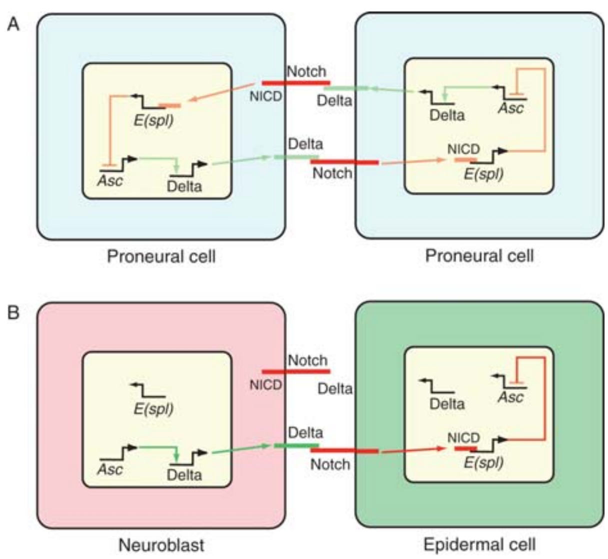


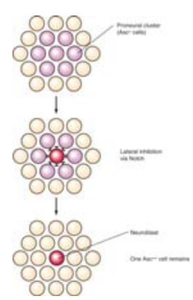
Birthdating studies:

- 3H-Thy incorporates into DNA in S phase
- It is available for ~2 hrs
- It is diluted by further cell divisions
- It can be detected with autoradiography
- It can tell us where neurons came from before migration
- It can tell us when neurons were "born"
- What does it NOT tell us?

Fig 3.3

Proneural genes experience Notch-Delta Lateral Inhibition





Notch/Delta interaction blocks neural fate in neighboring cells by blocking Asc via the E(spl) member Hes-1.

Fig. 1.28

Fig. 1.29

The cell cycle
elongates with age

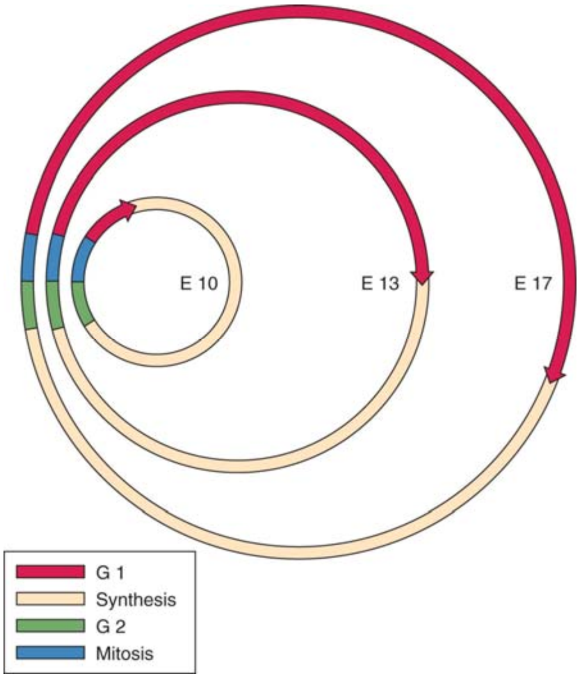
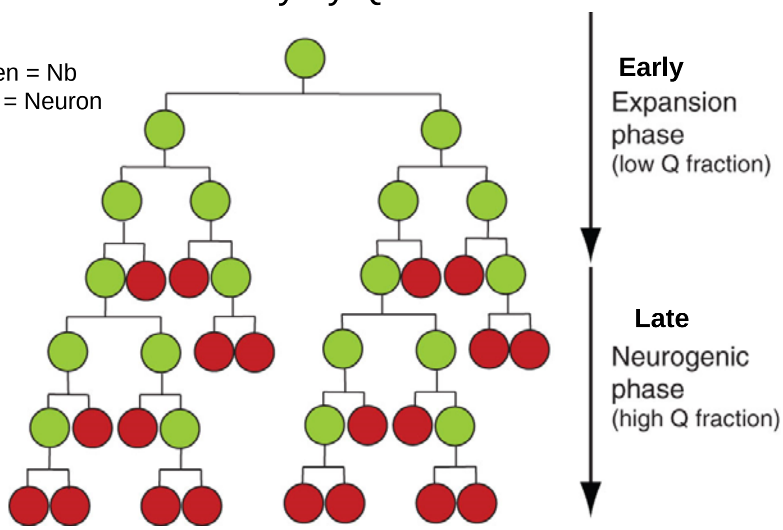


Fig 3.4

Neuroblast or terminal fate?
Assay by Q fraction msmt

Green = Nb
Red = Neuron



Terminal fate

Fig 3.5

Cell cycle control

- G1 to S phase (cyclinD/Cdk4) is well-controlled
- Cyclin binding to Cdks activates Cdks
- Cdks phosphorylate key proteins that push each next step
- Cdk Inhibitors p21 and p27 cause exit from cell cycle
- Rb is a tumor-suppressor protein that when active binds E2F1
- Rb is phosphorylated and IN activated by cyclinD/Cdk4
- Rb mutation (loss) frees E2F1 to push past the G1 to S restriction point of the cycle, possibly leading to tumor formation.

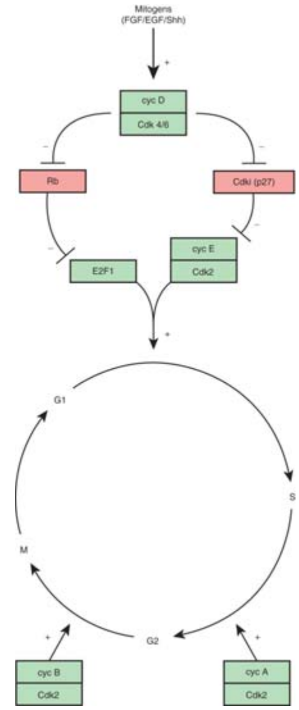


Fig 3.6

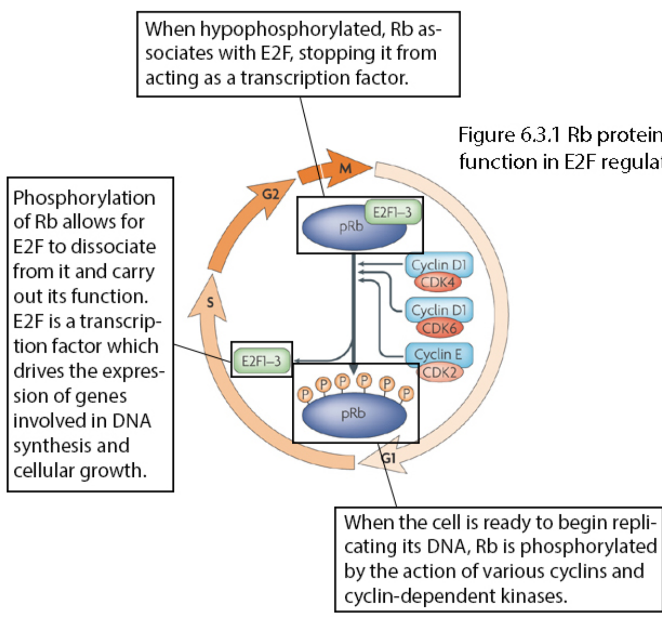


Figure 6.3.1 Rb protein's function in E2F regulation

Modified from Coller, Nature Reviews Molecular Biology; 8, 667-670. http://www.nature.com/nrm/journal/v8/n8/images/nrm2223-f2.jpg

Manipulating cell cycle genes in cerebral cortex

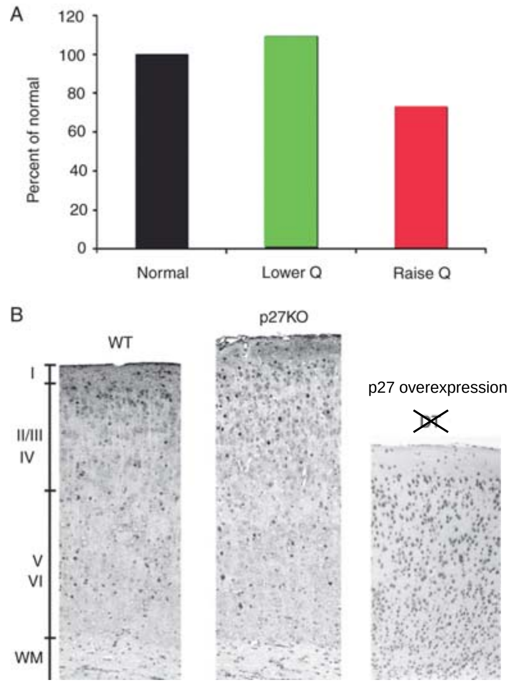
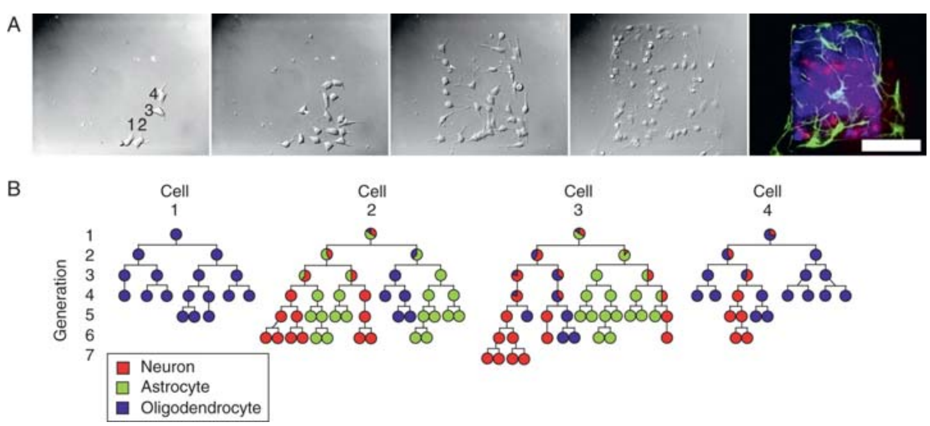


Fig 3.7

In vitro studies of proliferation show progressive restriction of fate



Multipotent progenitors are indeterminant in vitro and in vivo

Fig 3.8

Proneural genes and the Notch pathway

•Hes-1, Notch promote progenitor fate
•Hes-1 expression self-inhibits: oscillates in antiphase with proneural factors
•Proneural transcription factors promote expression of Notch ligands such as Delta
•Any slight imbalance in Notch ligand expression is amplified, leading to neural fate and suppression of neural fate in neighbors

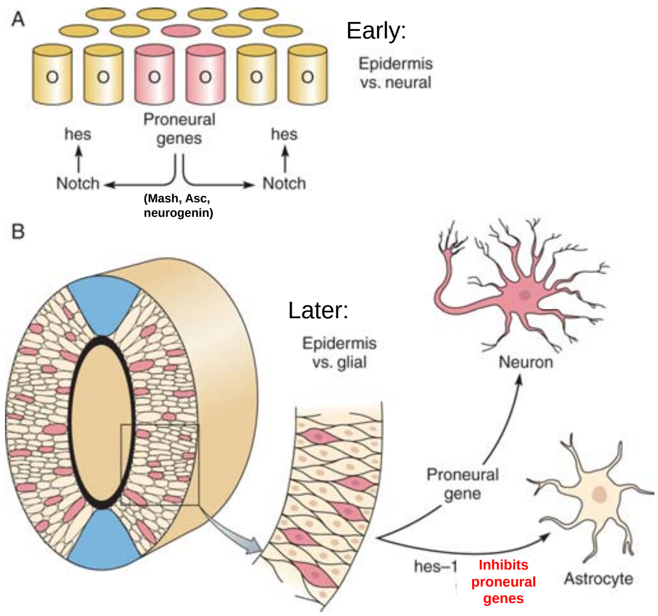


Fig 3.10

Notch-Delta signaling

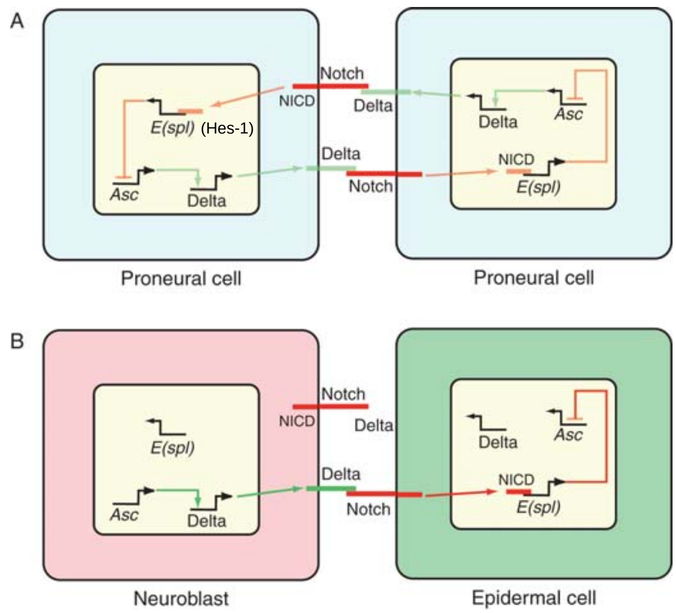


Fig. 1.28

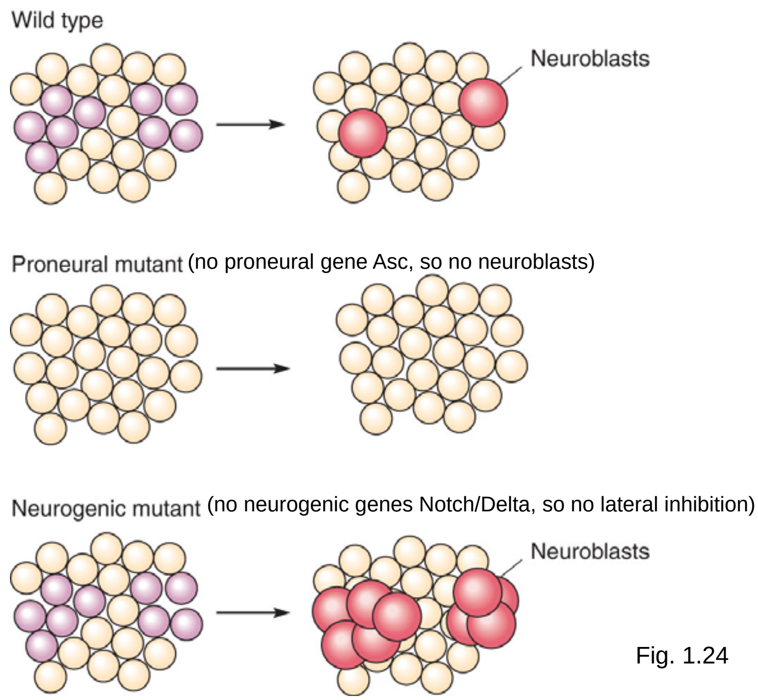


Fig. 1.24

Mitogens and GFs influence proliferation/fate

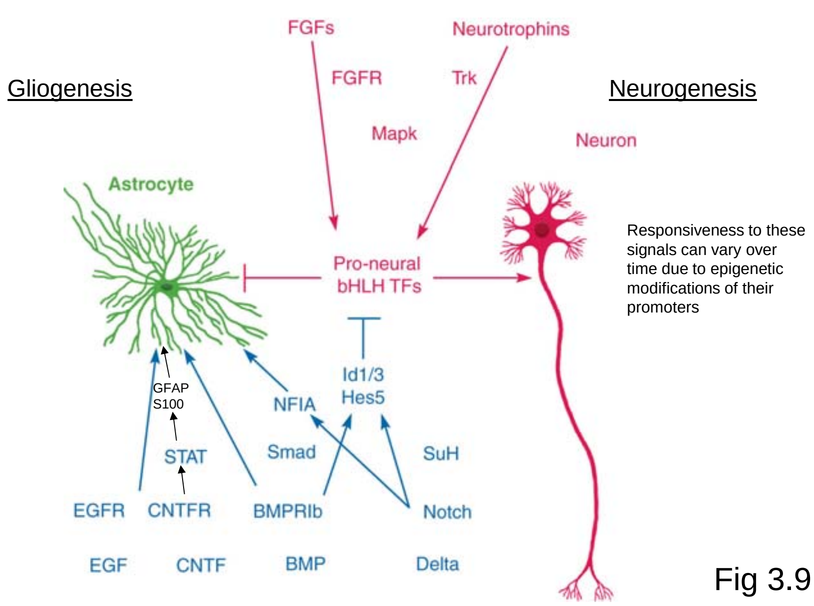


Fig 3.9

Oligodendrocyte development

Molecular switches alter fate
Note: Glial progenitors can produce neurons or glia

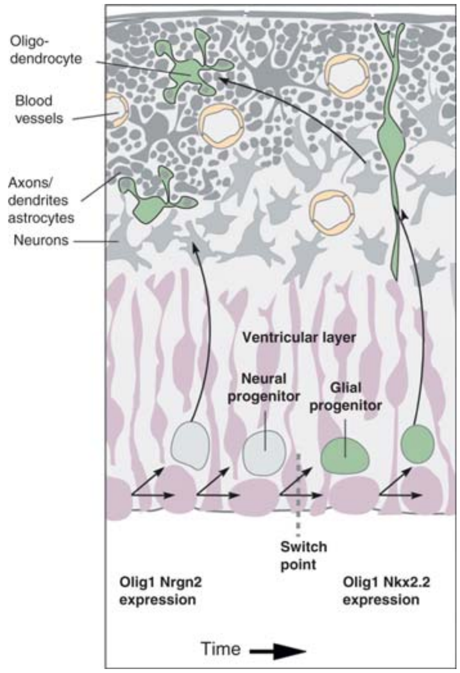


Fig 3.11

Neurogenesis in tadpole and adult frog retina

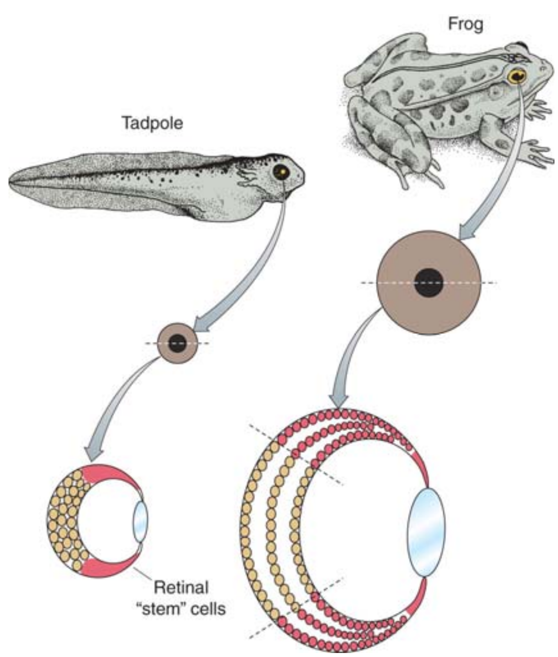


Fig 3.20

Adult Neurogenesis in Olfactory Bulb

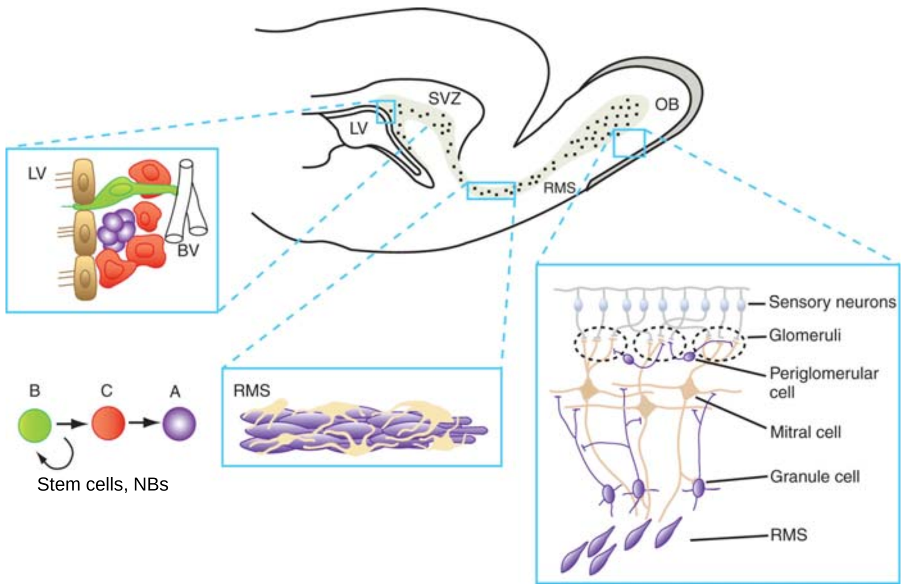


Fig 3.21

Adult Neurogenesis in Mouse Hippocampus
Are new neurons functional?

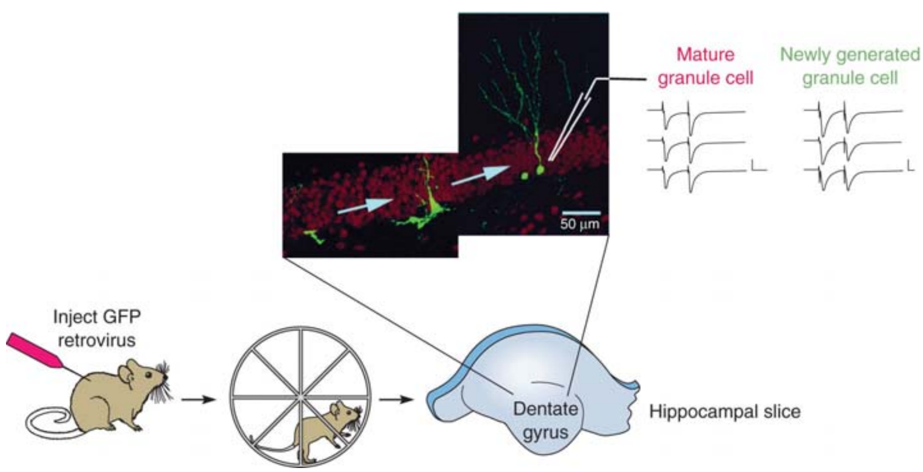


Fig 3.22

Cortical cytoarchitecture

Fig 3.12

^{3}H-thymidine birthdating technique

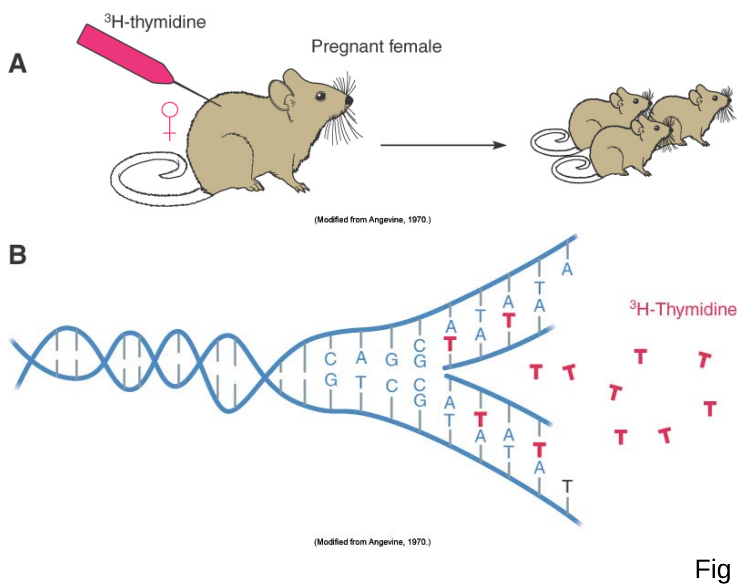
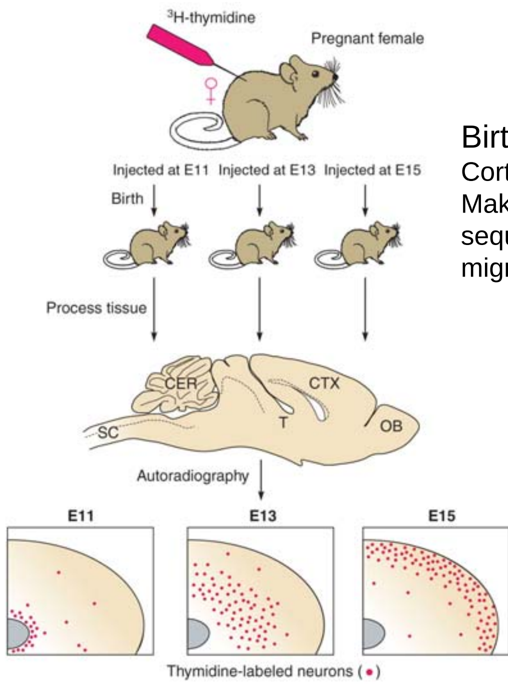


Fig 3.3



Birthdating studies:
Cortical Histogenesis-
Making layers in an inside-out sequence of neurogenesis and migration

Fig 3.3

Cortical Histogenesis: Making layers (monkeys)

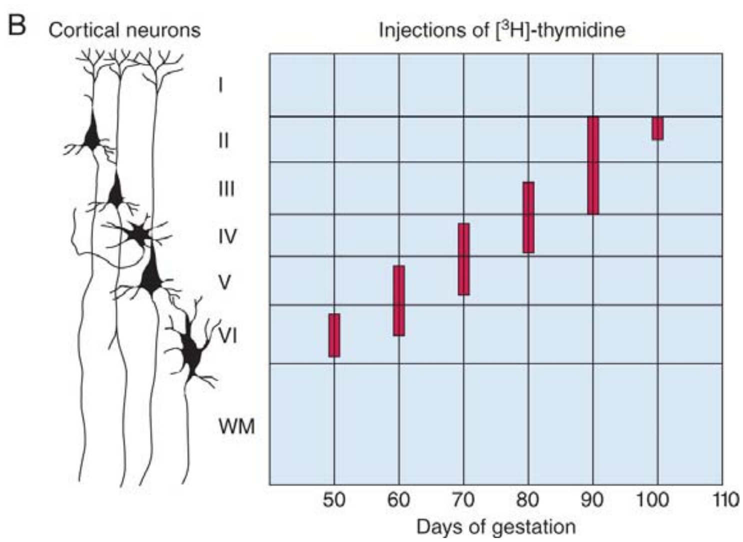


Fig 3.3

Cortical Histogenesis

3 stages:
1. Preplate formation
   1. Cajal-Retzius cells
   2. Subplate cells
2. Cortical plate splits the preplate
3. Formation of 6 layers in an inside-out order

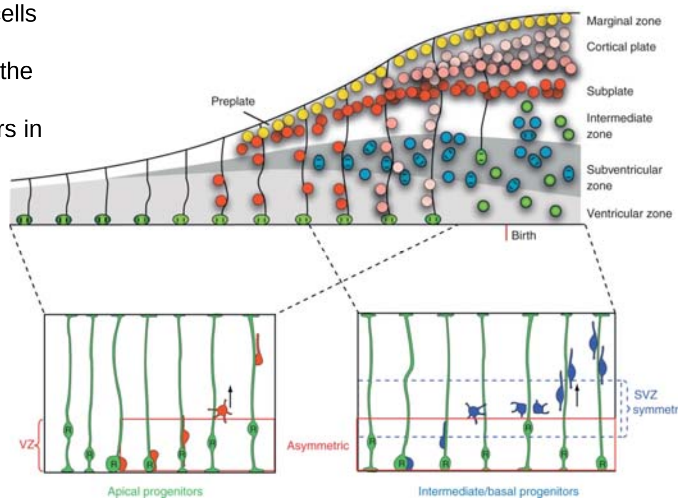


Fig 3.13

Radial glia (IPCs) guide migration and generate neurons

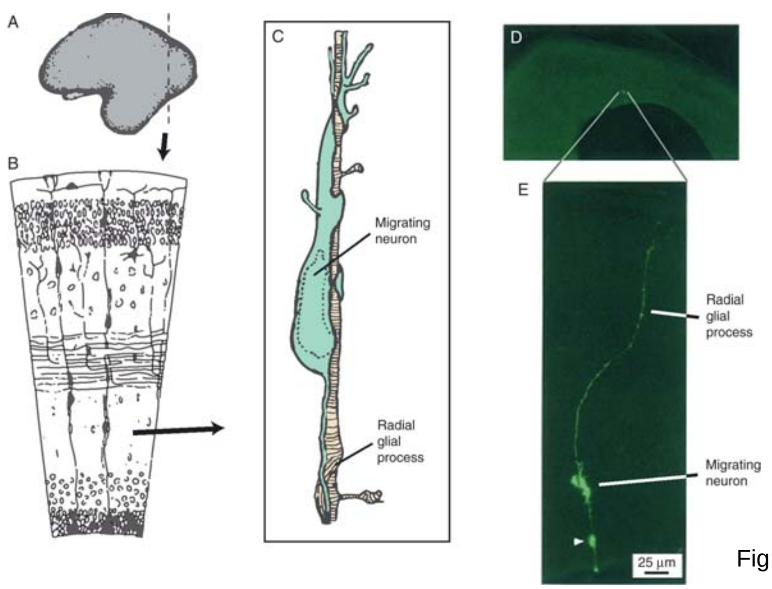


Fig 3.14

Genesis and Migration of Cortical GABA Neurons

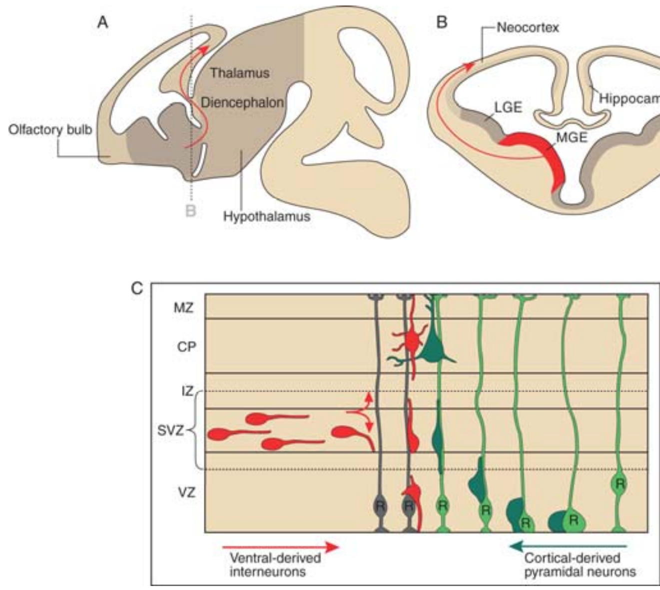
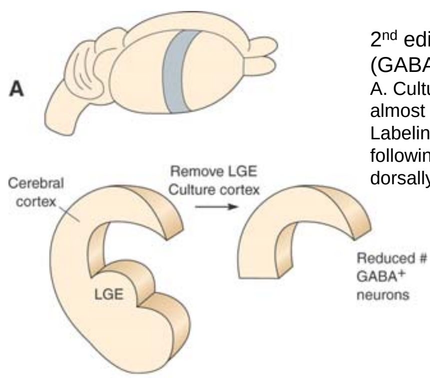
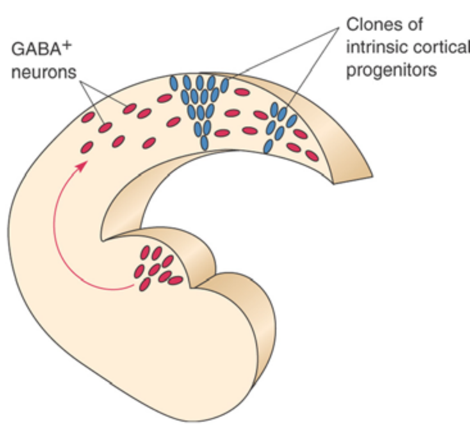


Fig 3.15



2nd edition Fig 3.20 Origin of Cortical Inhibitory (GABAergic) neurons.

A. Culturing cerebral cortex without ventral telencephalon almost eliminates GABAergic neurons from cortex. B. Labeling a small population of precursor cells in LGE and following their migratory path and fate shows that they migrate dorsally and contain GABA.



Cerebellar Histogenesis

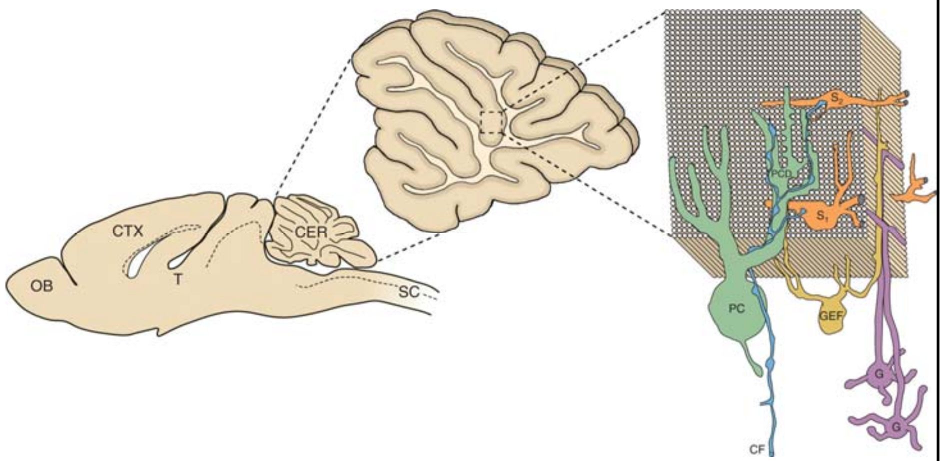


Fig 3.16

Cerebellar Histogenesis

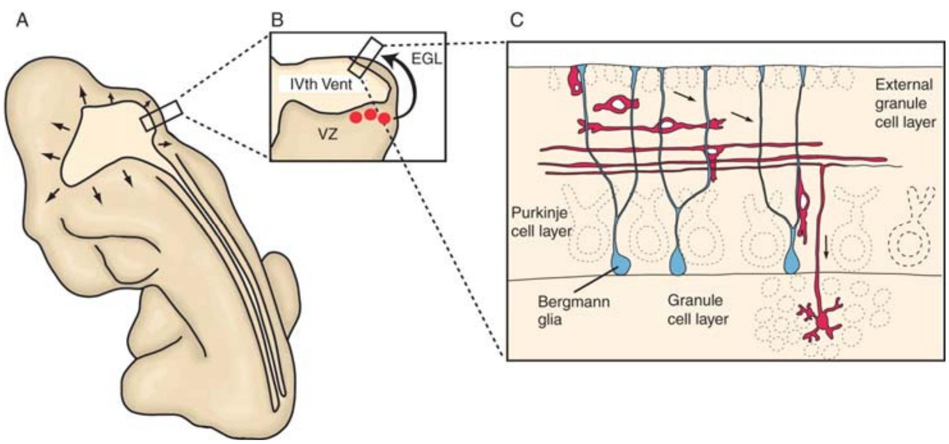
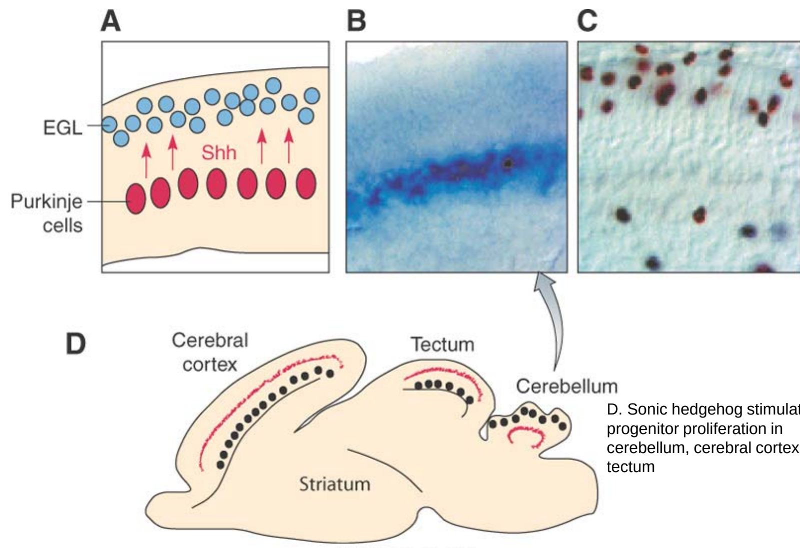


Fig 3.17

A-C. Cerebellar Purkinje neurons produce Shh (A-red, B-blue), which is detected by receptors ptc and smo in the granule cell neurons (A-blue, C- brown), promoting the proliferation of matching numbers of granule cell neurons.



D. Sonic hedgehog stimulates progenitor proliferation in cerebellum, cerebral cortex, and tectum

(Modified from Ruiz; Altaba, 2002.)

2nd ed. Fig 3.10

Reelin Function

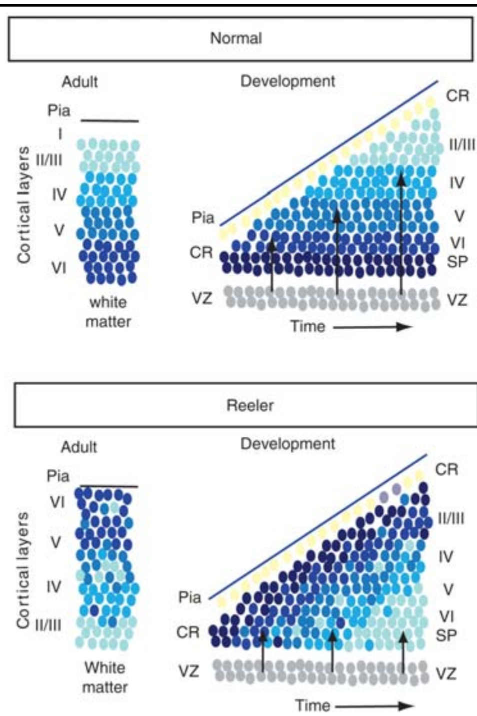


Fig 3.18

Reelin Function

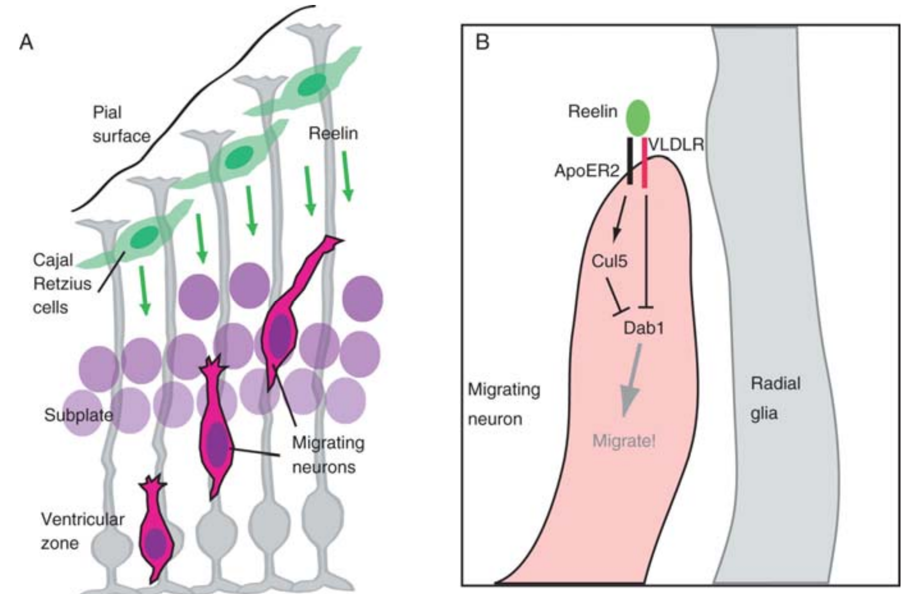


Fig 3.19

Neural Crest Migration

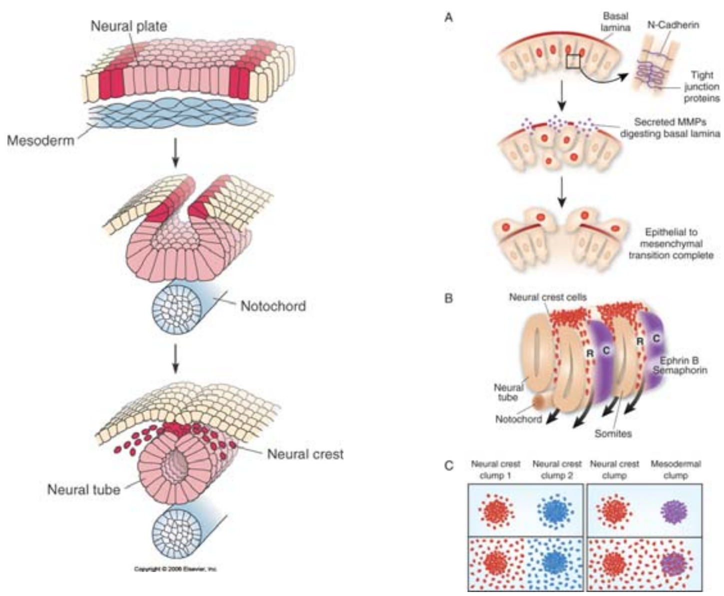


Fig 3.23

Chick-quail chimera method of Nicole LeDouarin