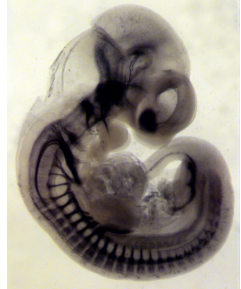


Development of the CNS



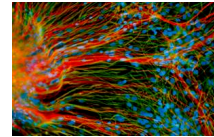
Lori Zeltser lz146@columbia.edu

Why study CNS development?

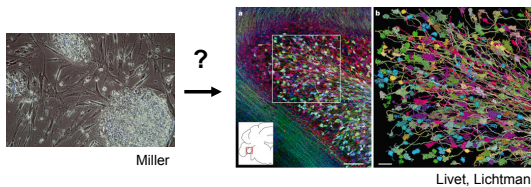
To design better strategies to prevent/treat disorders of CNS development.



To serve as the foundation for efforts to treat neurological diseases/injury with stem cell-based therapies.



The Challenge



How to Make a Nervous System

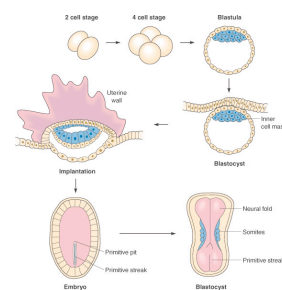
- Neural induction
- Neural tube formation
- Acquisition of a positional identity
- Birth, migration & differentiation of neurons and glia
- Axonal pathfinding and connectivity
- Binding of trophic factors for survival and differentiation
- Synapse formation, refinement and plasticity

How to Make a Nervous System

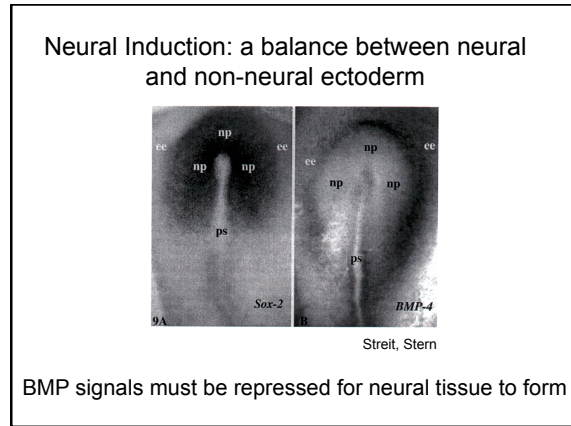
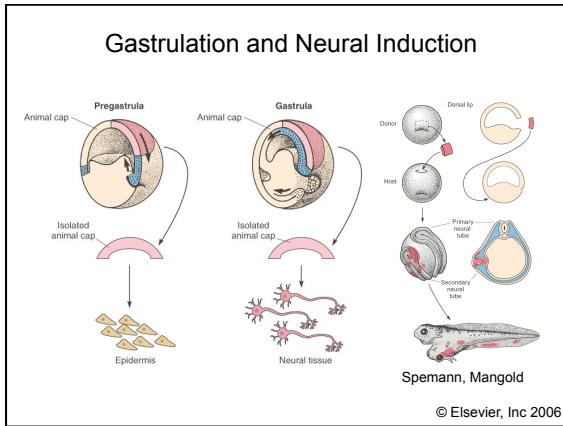
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“The most important time in your life is not birth, marriage, or death, but gastrulation”

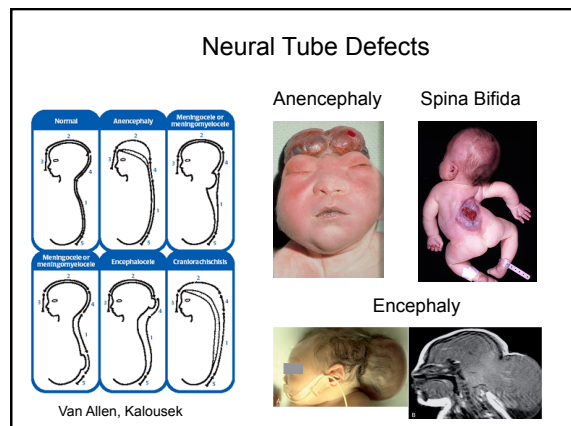
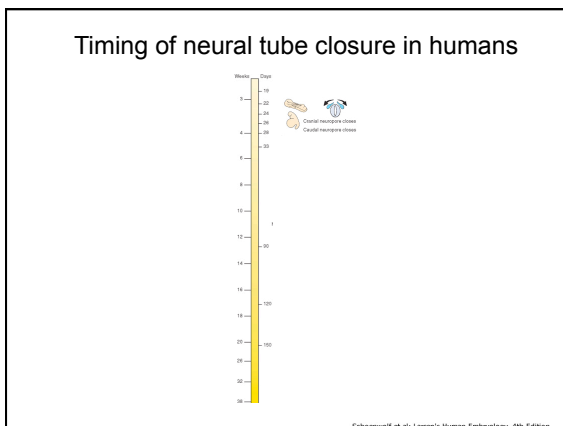
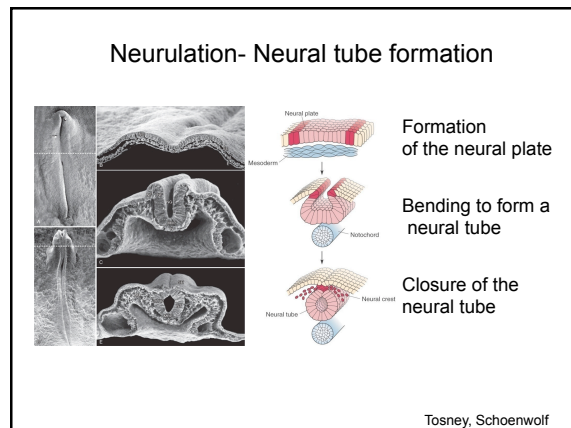
- Lewis Wolpert



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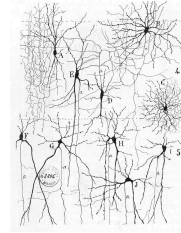
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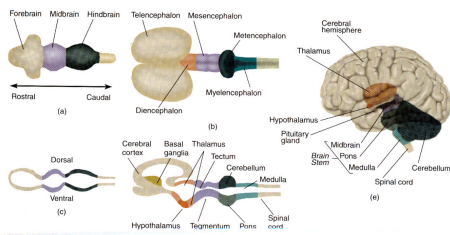
Generation of neuronal diversity



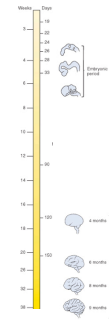
Ramon y Cajal

1. Patterning: acquisition of a positional identity
2. Differentiation: functionally distinct cell types

Differentiation of neural tube to form distinct vesicles

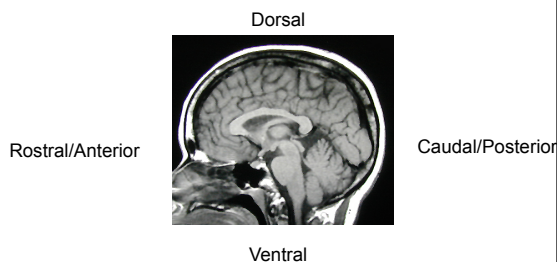


Timing of CNS development in humans



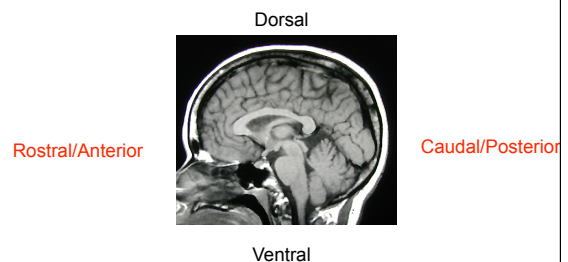
Schoenwolf et al.: Larsen's Human Embryology, 4th Edition

Patterning: acquisition of a positional identity

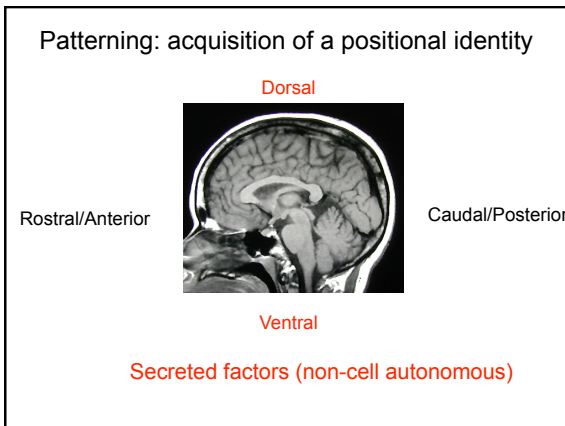
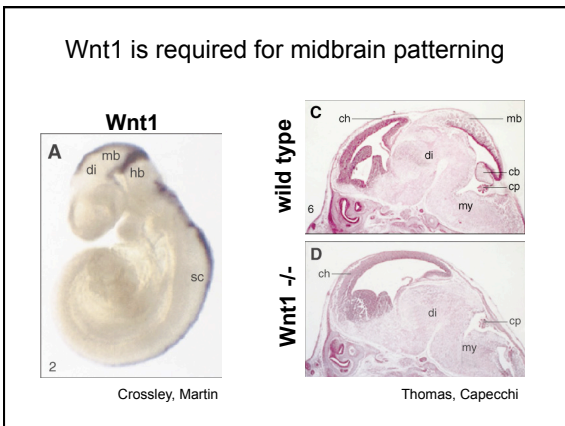
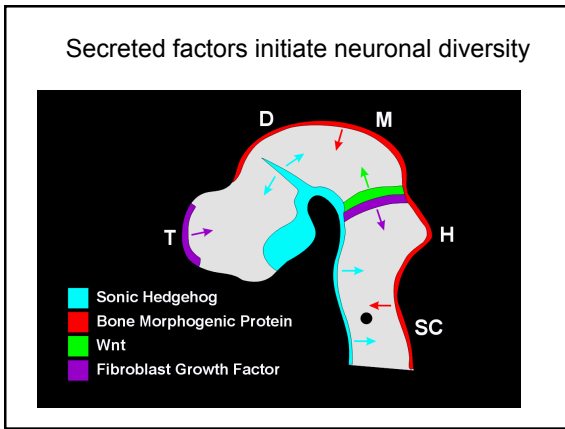
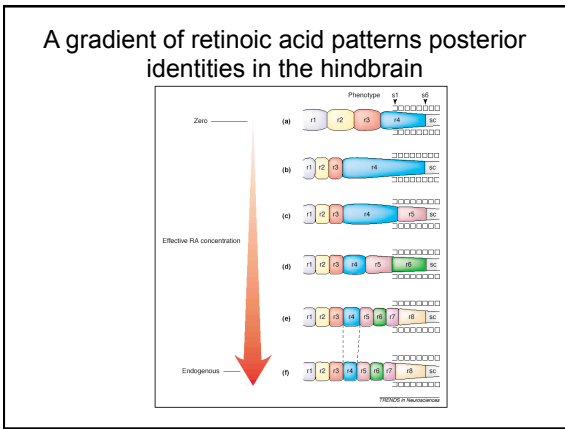
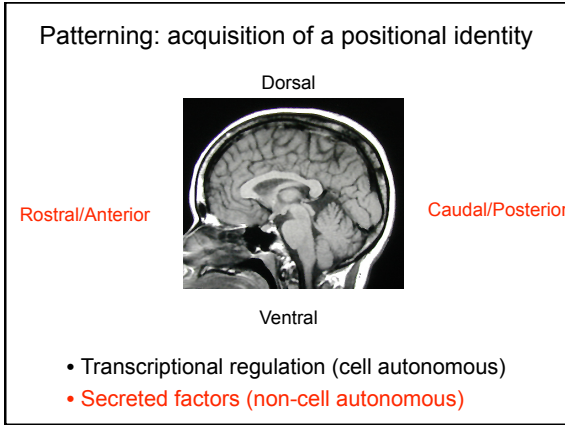
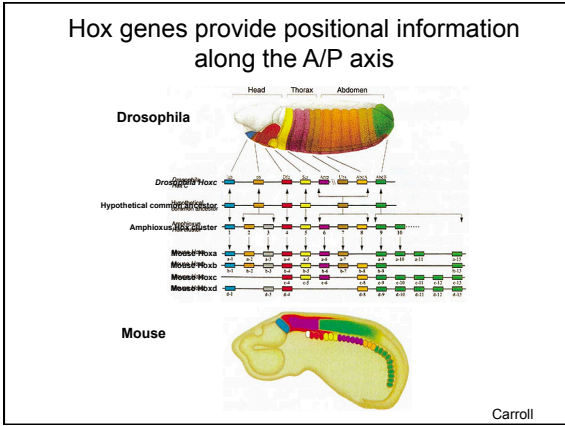


- Transcriptional regulation (cell autonomous)
- Secreted factors (non-cell autonomous)

Patterning: acquisition of a positional identity



- Transcriptional regulation (cell autonomous)
- Secreted factors (non-cell autonomous)



Secreted factors initiate neuronal diversity

■ Sonic Hedgehog
■ Bone Morphogenic Protein
■ Wnt
■ Fibroblast Growth Factor

A gradient of Shh patterns ventral identities

Shh

Roelink, Ericson, Briscoe, Jessell

Two Signaling Centers Specify Neural Cell Types along the DV axis

Dorsal Signaling Center
 Roof Plate
 BMP/TGFβ

Ventral Signaling Center
 Notochord and Floor Plate
 SHH

Jessell

Ventral patterning defect: Holoprosencephaly

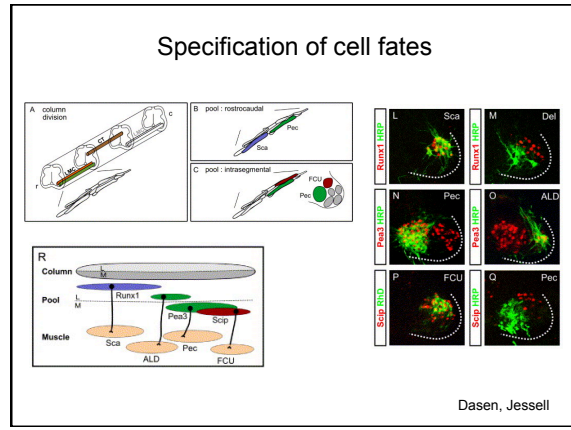
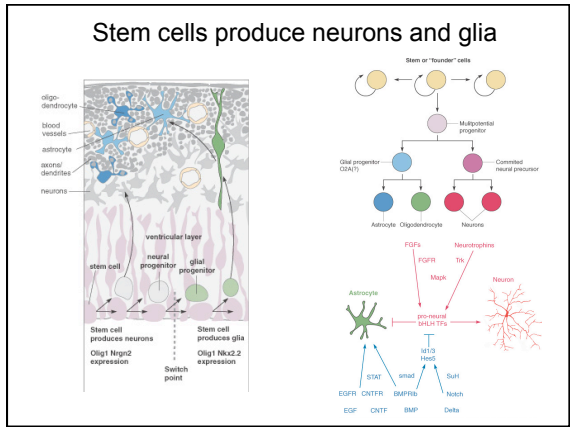
Gripp, Elledge

How to Make a Nervous System

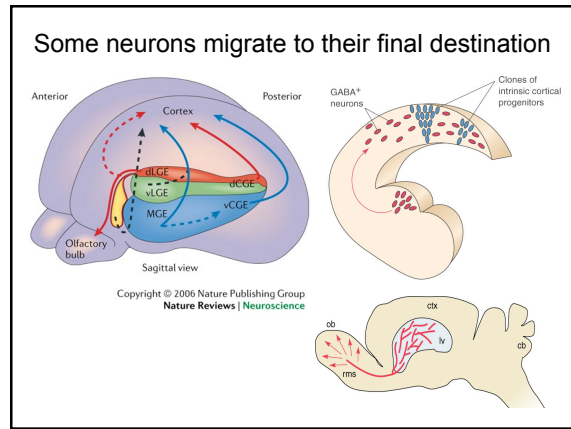
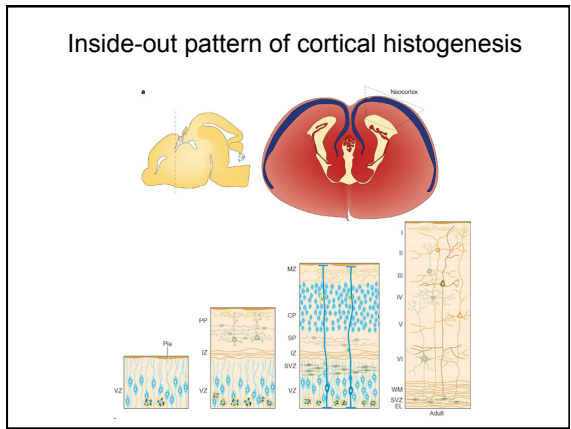
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Differentiation of the walls of the neural tube

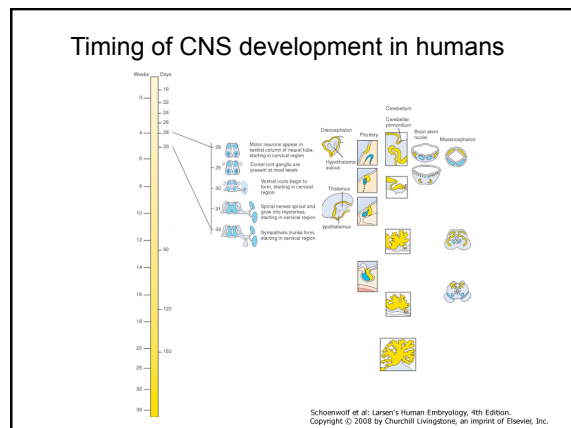
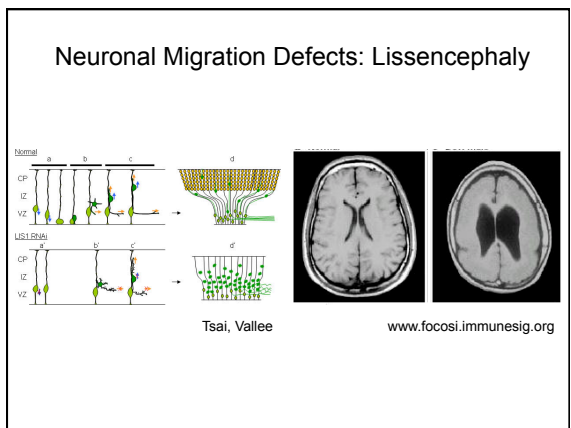
Scheerwolf et al., Larson's Human Embryology, 4th Edition, Copyright © 2008 by Churchill Livingstone, an imprint of Elsevier, Inc. All rights reserved.



Dasen, Jessell



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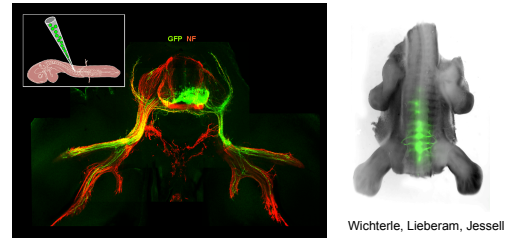


Schoenwolf et al. Larsen's Human Embryology, 4th Edition.
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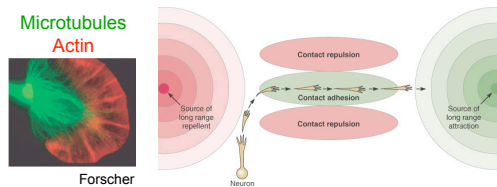
Specification of axonal connectivity



Wichterle, Lieberam, Jessell

1. Pathway selection (route to target area)
2. Target selection (bind to appropriate target cells)
3. Address selection (refine/prune initial pattern)

Guidance by specific growth cone adhesion and repulsion



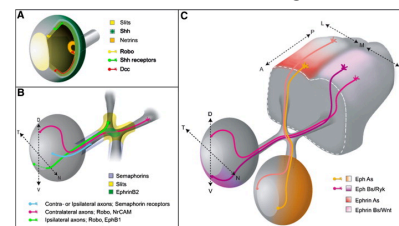
Permissive extracellular matrix protein: laminin

Repulsive cues: ephrins and semaphorins

Long range attractive cues: netrins

Secreted repulsive cues: slits

Guidance of Retinal Ganglion Axons

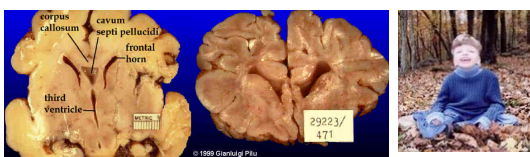


Retina: Slits, Shh and CAMs direct growth to optic disc; netrin guides axons out of the eye.

Optic chiasm: semaphorins, slits and Shh constrain axons to optic nerve; ephrins prevent ipsilateral axons from crossing; contralateral axons so not express receptor

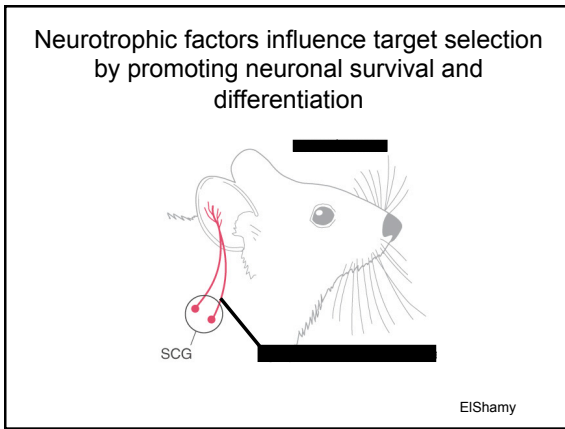
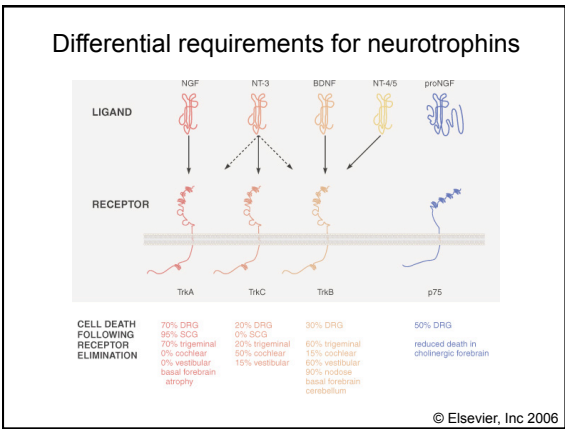
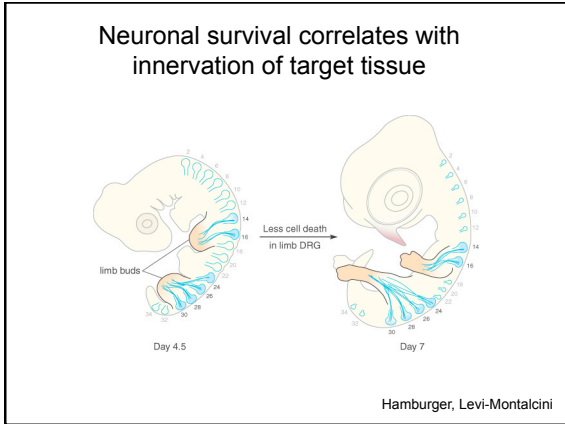
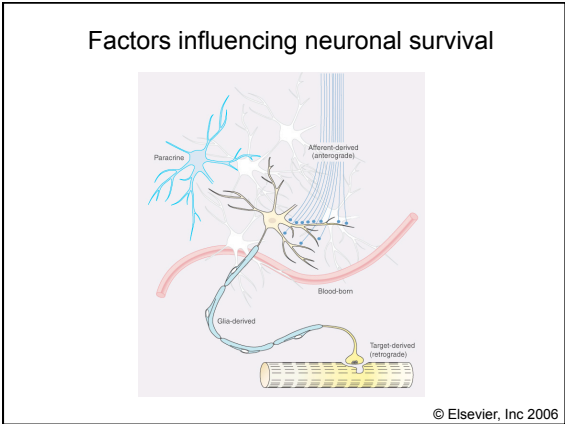
Topographic mapping in the superior colliculus: gradients of Ephrins (ephrinA for A-P axis and ephrinB for M-L axis)

Axon guidance defects: Agenesis of the corpus callosum



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