Cerebrospinal fluid absorption: do we understand the basics ?

Miles Johnston, Ph.D.
Andrei Zakharov, M.D.
Christina Papaiconomou, Ph.D. student

Neuroscience Research
Department of Laboratory Medicine and Pathobiology
Sunnybrook and Women's College HSC
University of Toronto

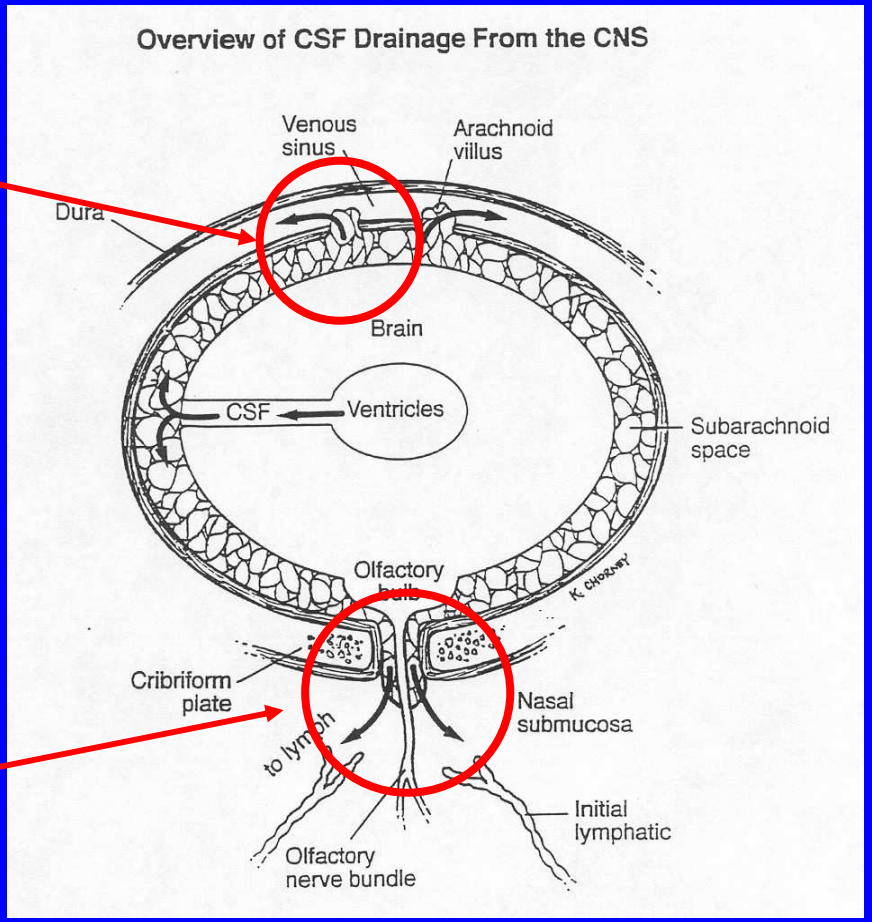
Hydrocephalus

The fabric on which current views of hydrocephalus are based has been distorted by the arachnoid-centric view of CSF transport.

Arachnoid granulations and villi

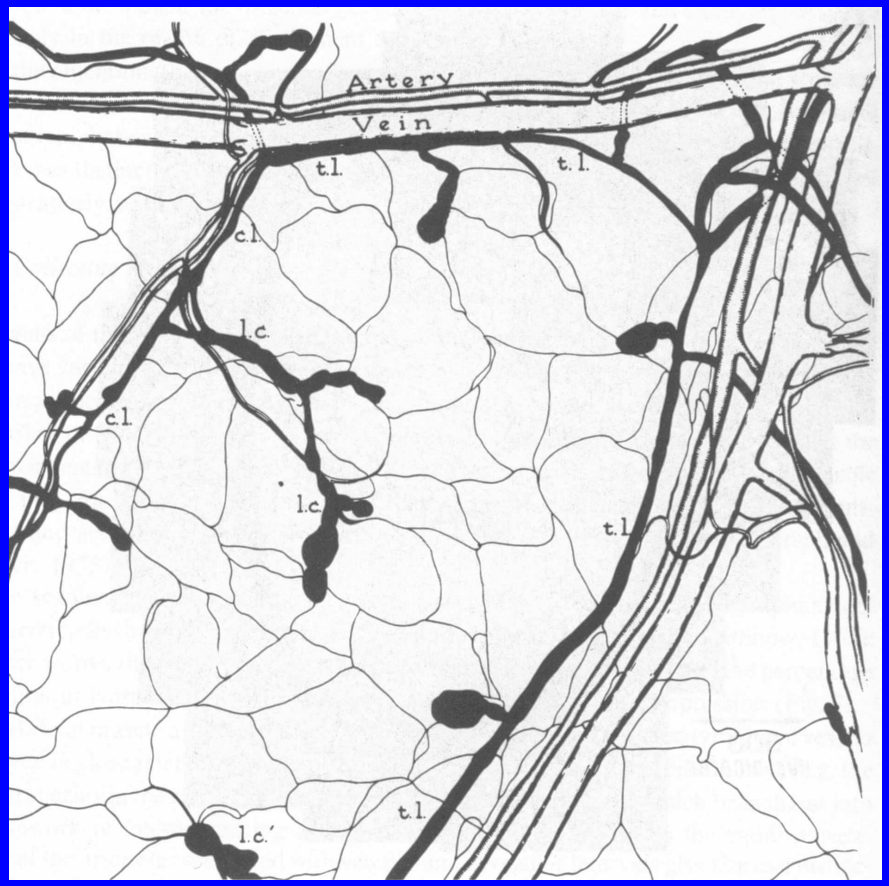
-quantitative support?
-developmental issues?
-pressure gradient?
-association with veins?
-venous blockage/hydrocephalus?
-agenesis/hydrocephalus?
-obstruction and ventriculomegaly?

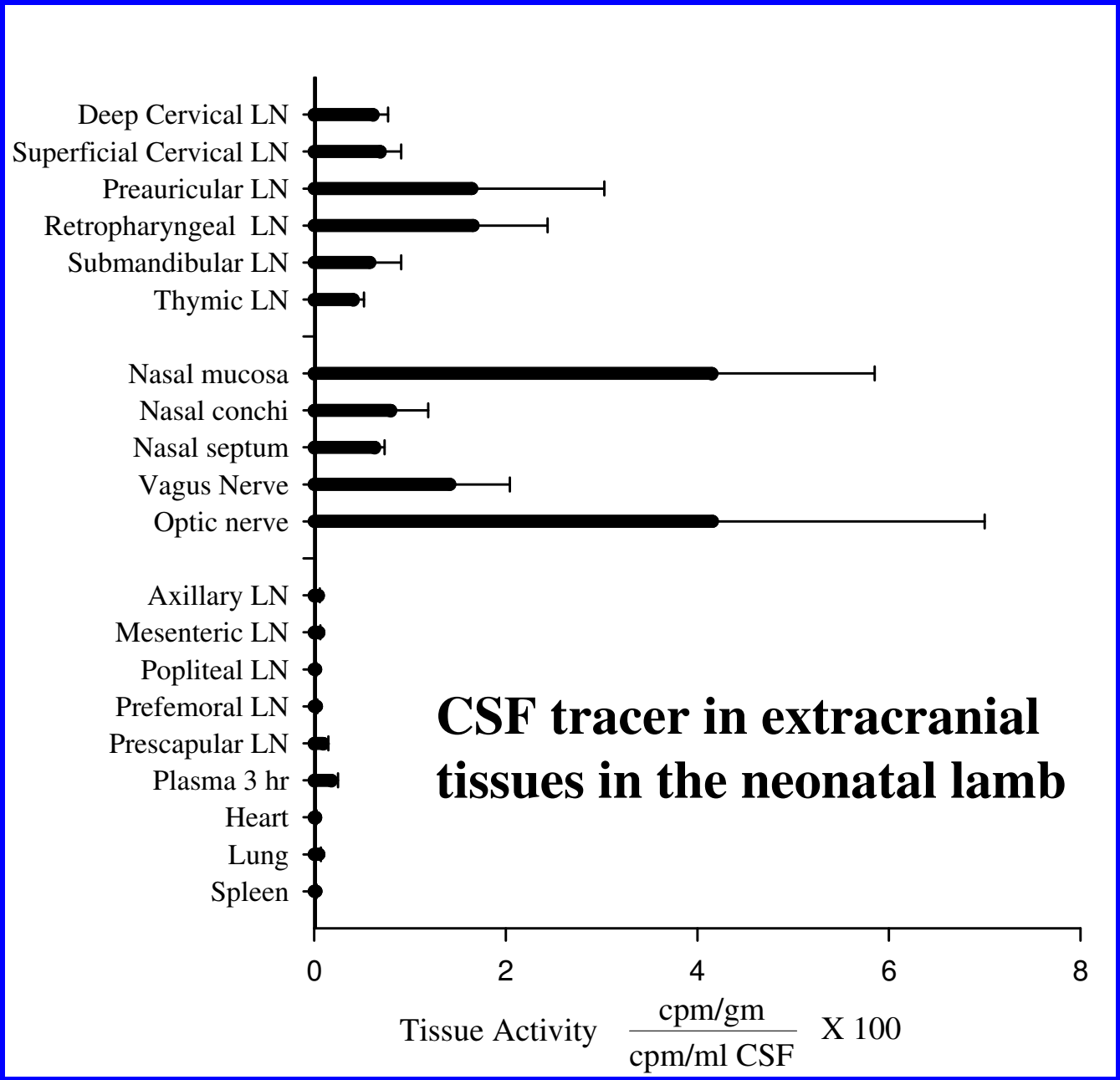
An alternative lymphatic Approach to CSF transport



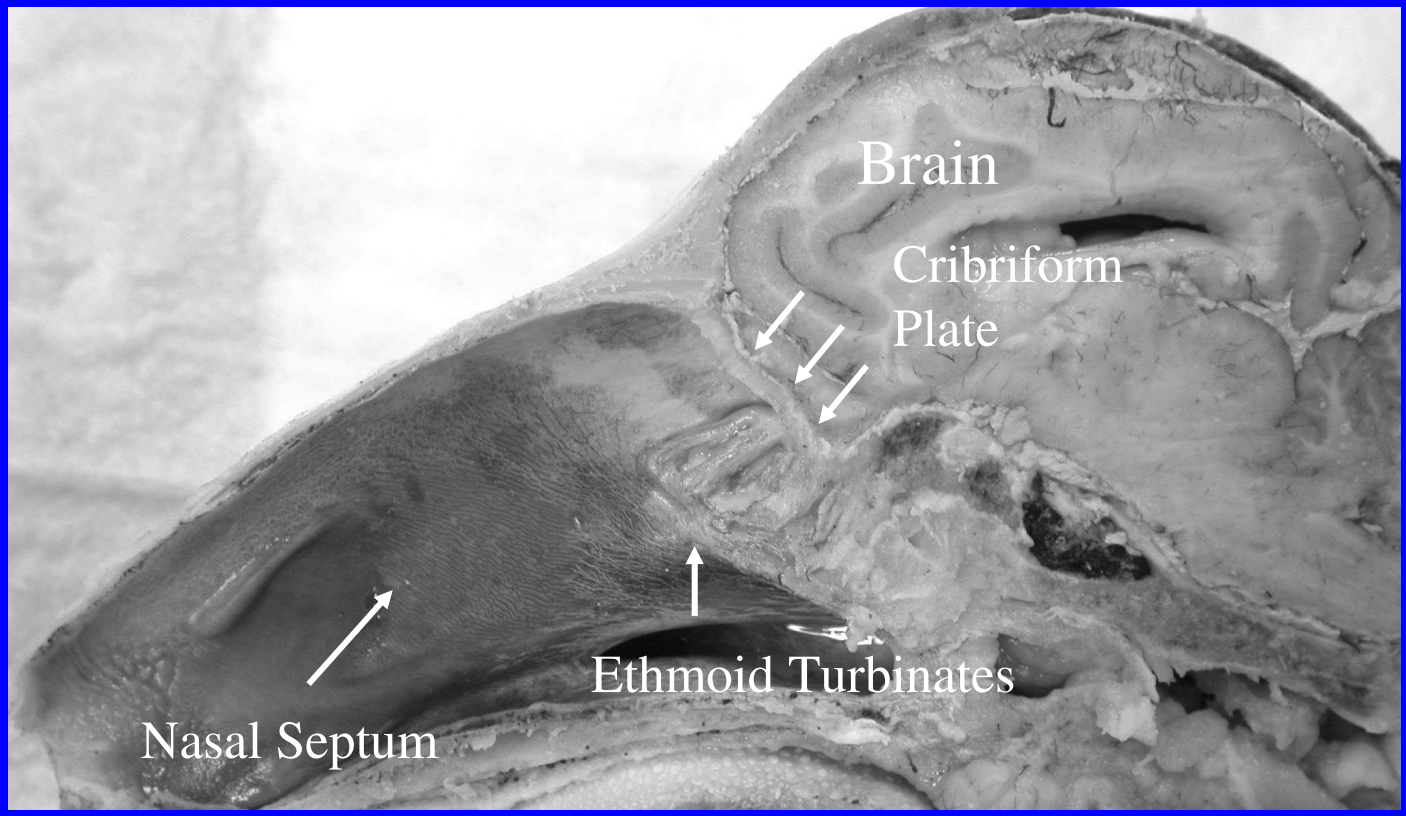
Lymphatic System

No lymphatic vessels within CNS parenchyma




Deep Cervical LN
Superficial Cervical LN
Preauricular LN
Retropharyngeal LN
Submandibular LN
Thymic LN
Nasal mucosa
Nasal conchi
Nasal septum
Vagus Nerve
Optic nerve
Axillary LN
Mesenteric LN
Popliteal LN
Prefemoral LN
Prescapular LN
Plasma 3 hr
Heart
Lung
Spleen
0
2
4
6
8
Tissue Activity cpm/gm / cpm/ml CSF X 100
CSF tracer in extracranial tissues in the neonatal lamb

CSF transport by lymphatic vessels



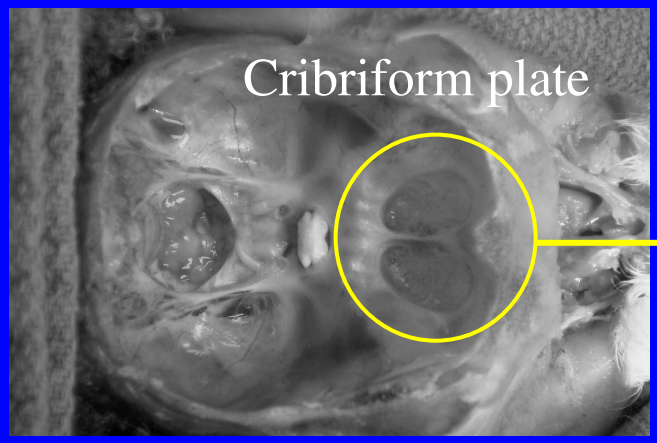
Microfil
(post-mortem)

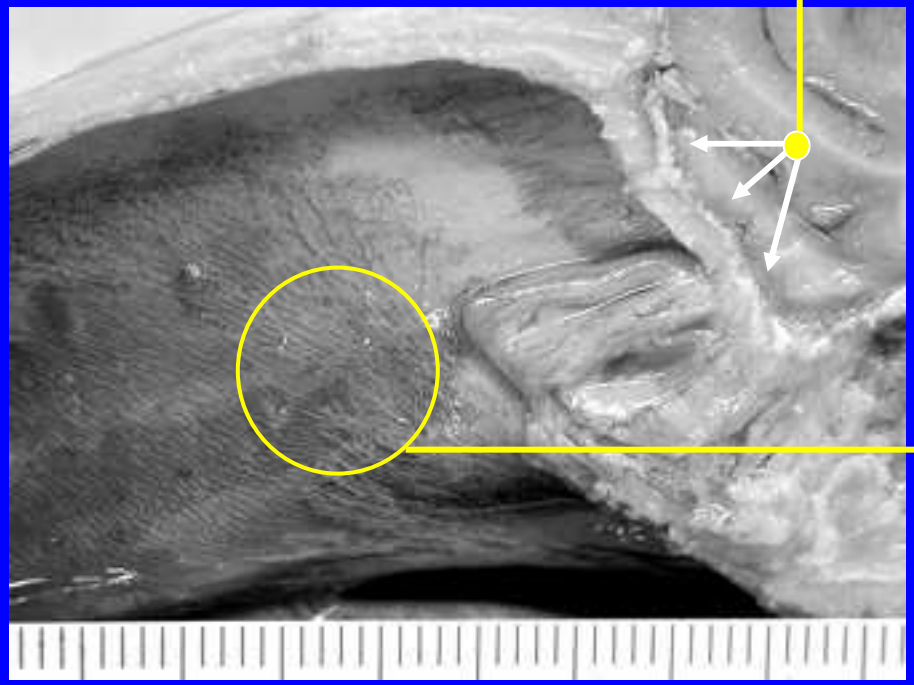
Subarachnoid compartment

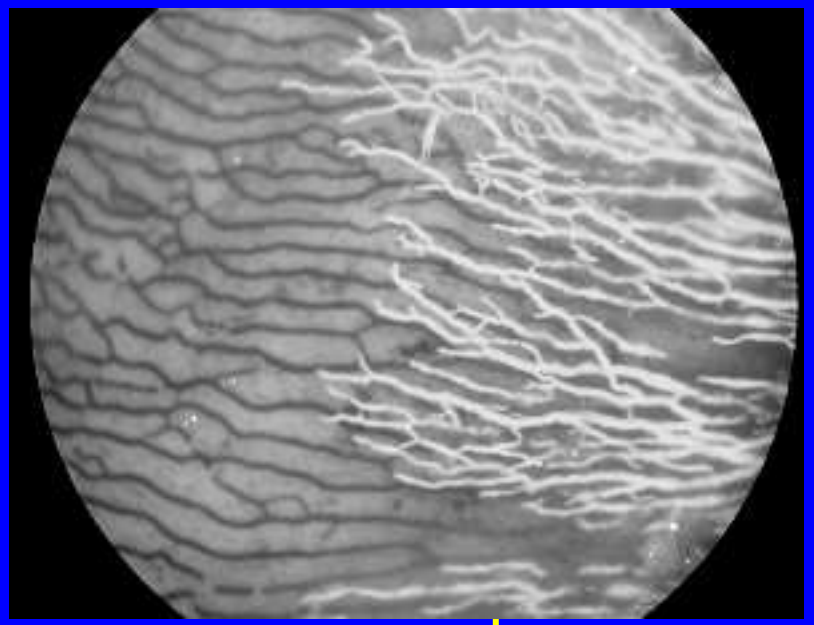
Microfil - Silicone Rubber

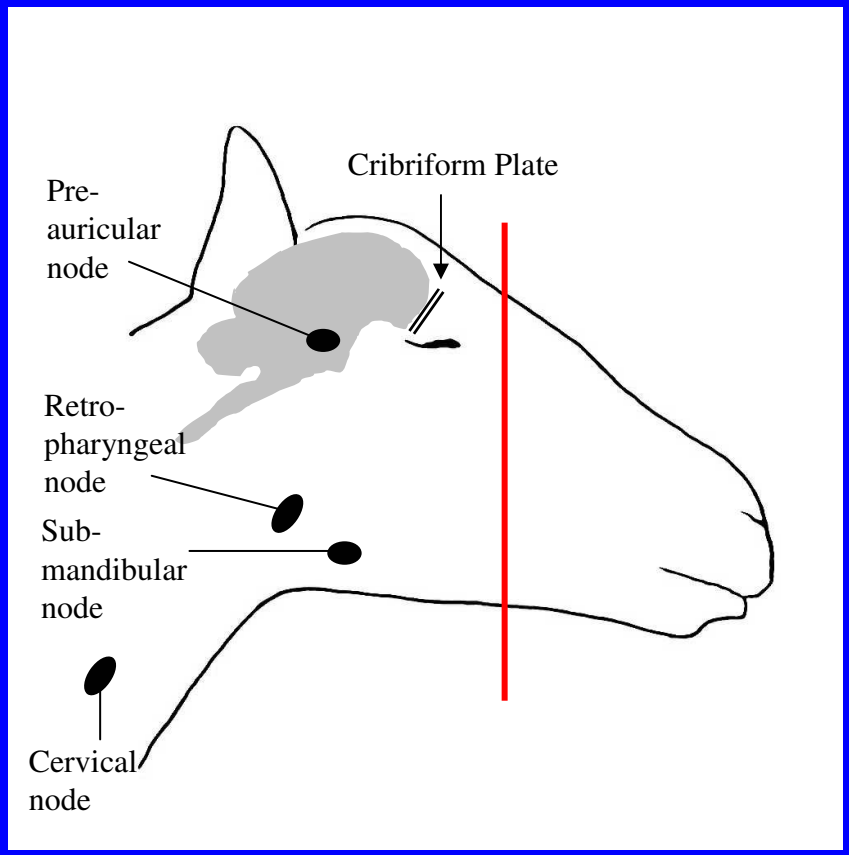
Injection Compound

Presence of Microfil in Paranasal lymphatics



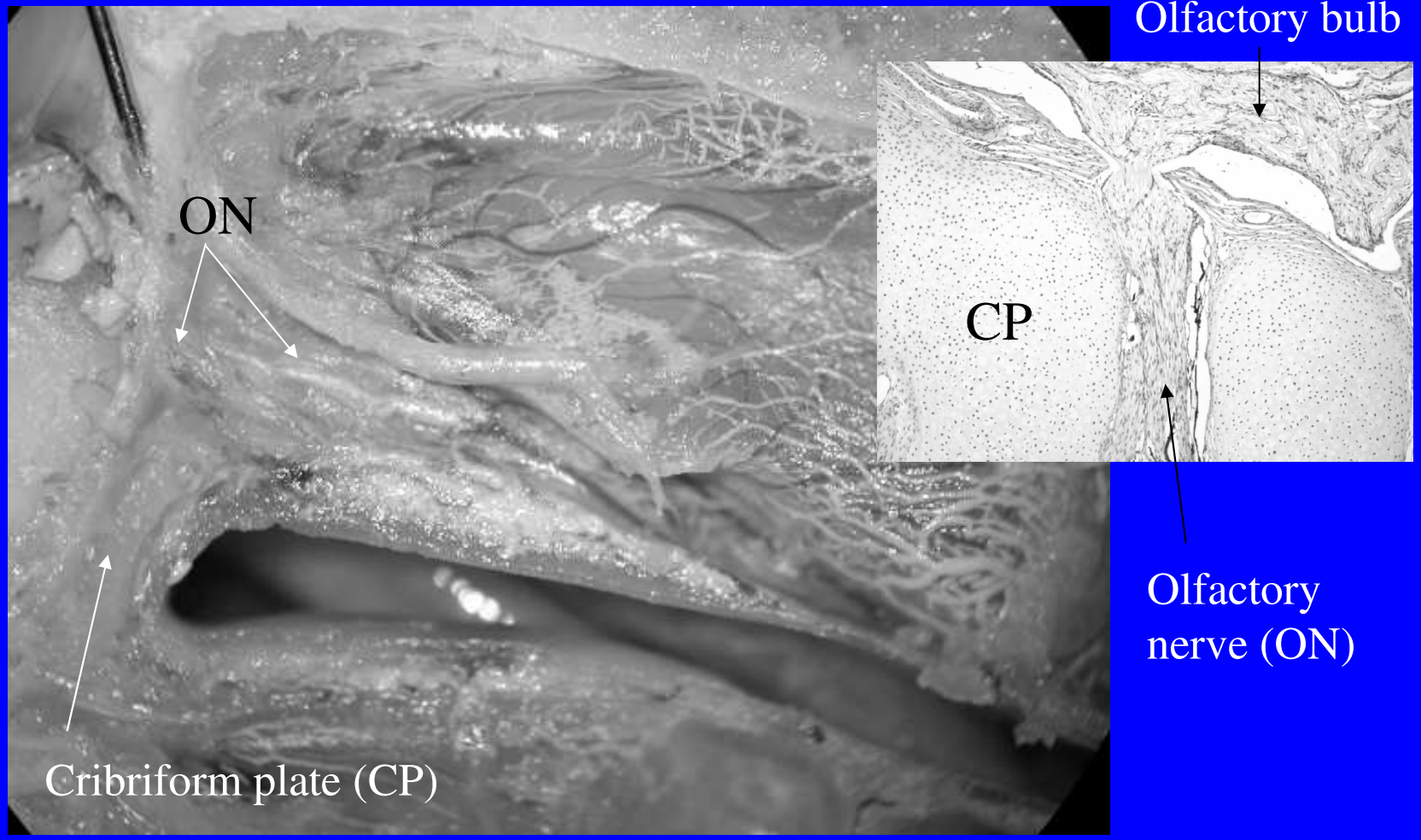


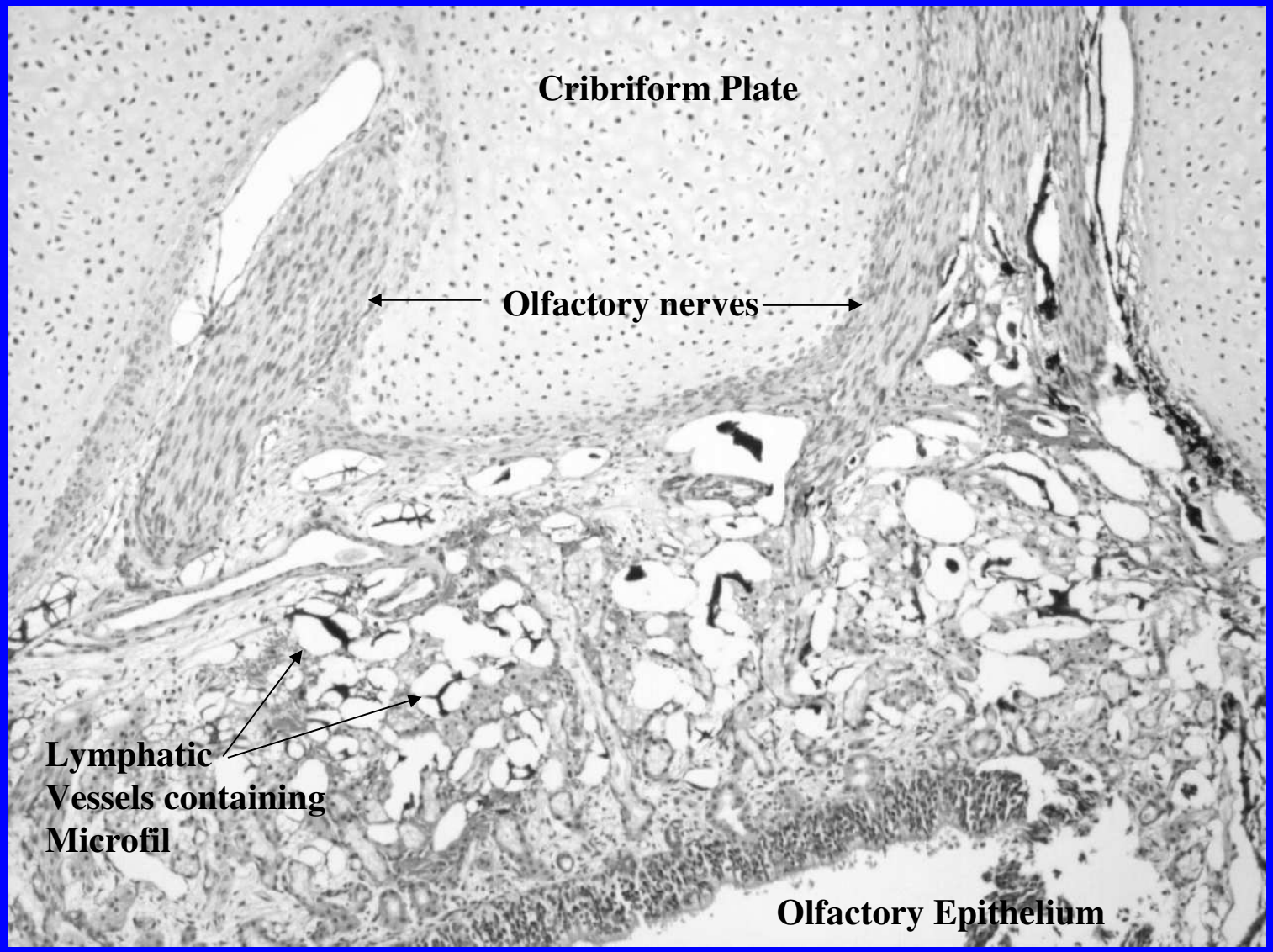


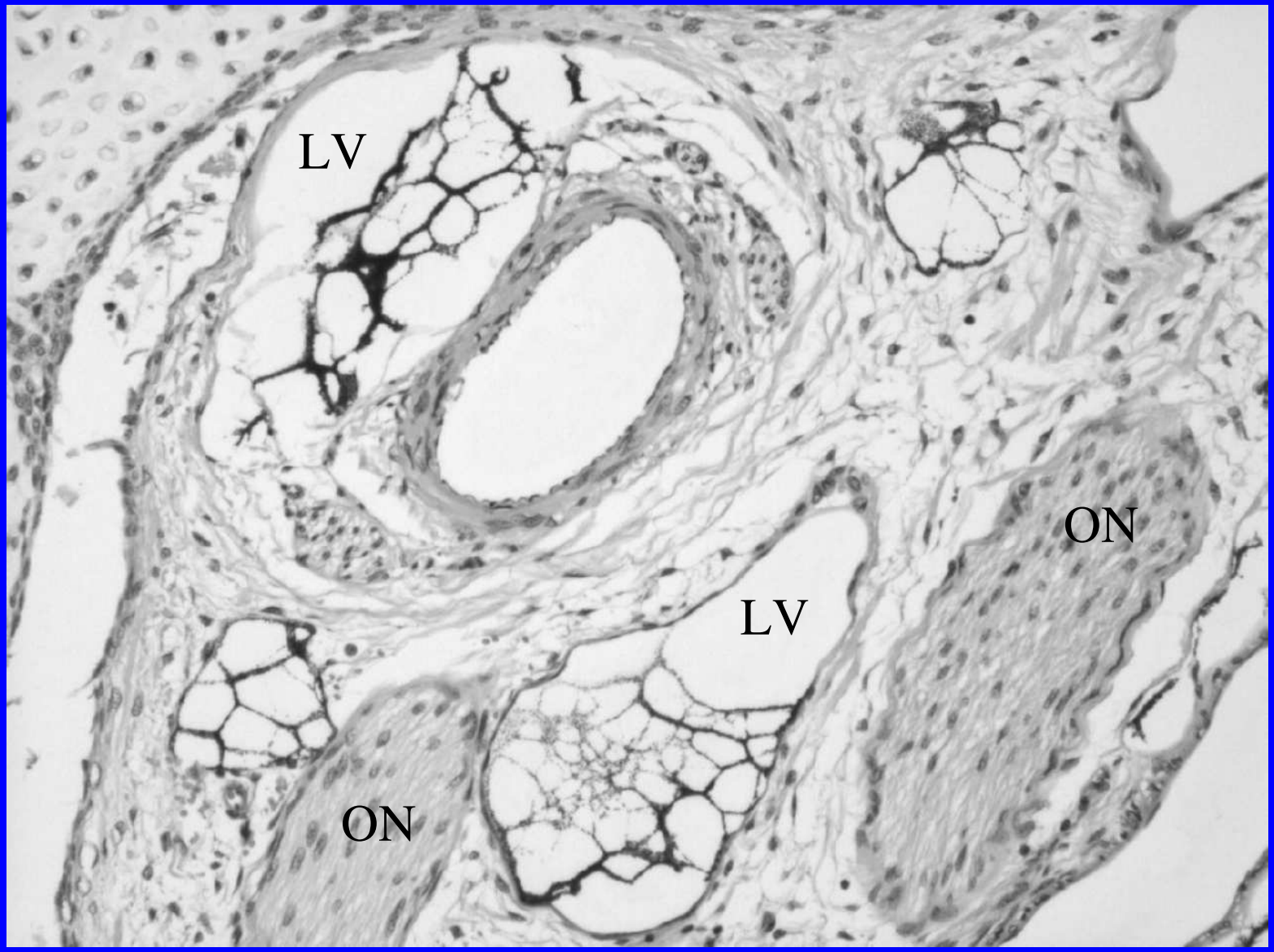


Microfil in extensive lymphatic networks in the ethmoid turbinates

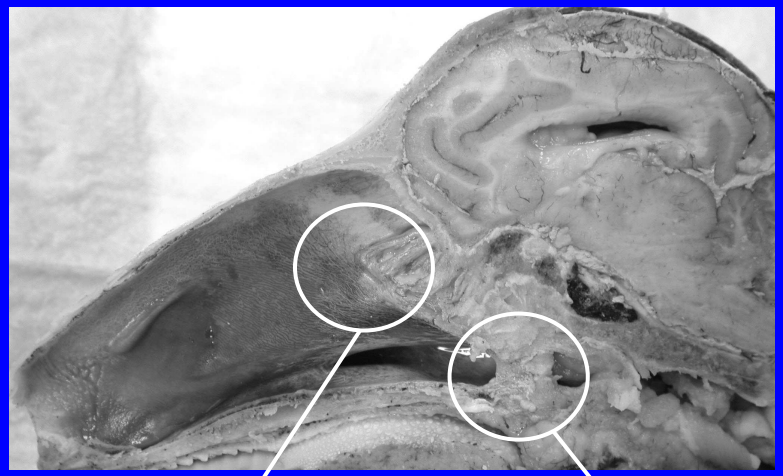
Olfactory nerve-lymph connections



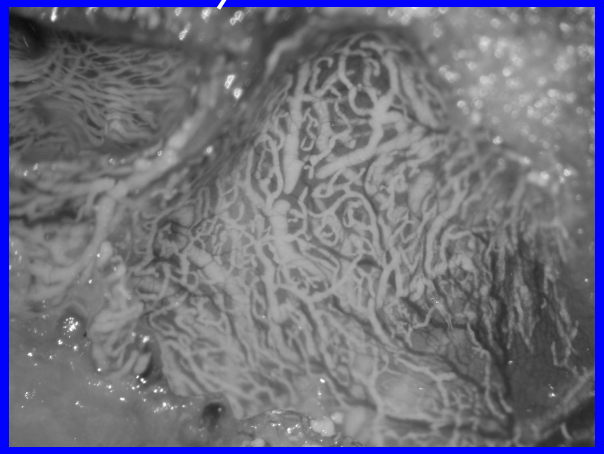

Cribriform Plate
Olfactory nerves
Lymphatic
Vessels containing
Microfil
Olfactory Epithelium

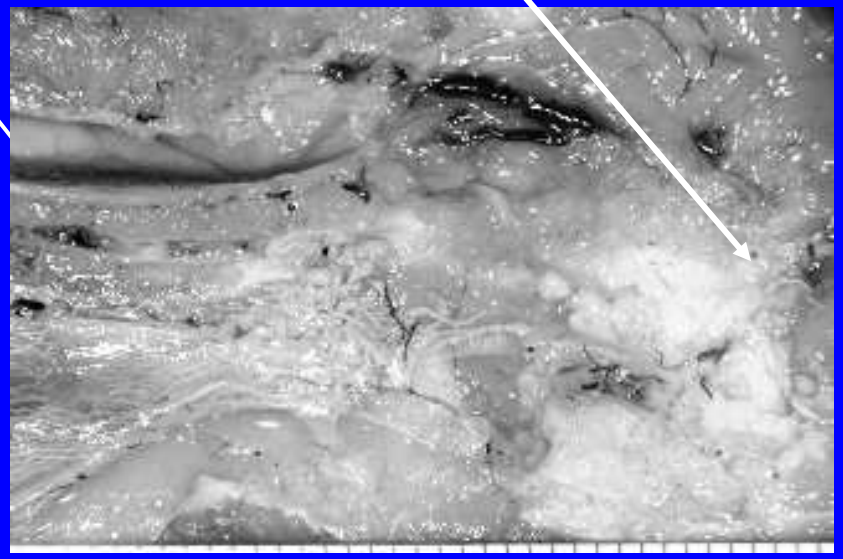

LV
ON
LV
ON

CSF transport by lymphatic vessels to regional lymph nodes

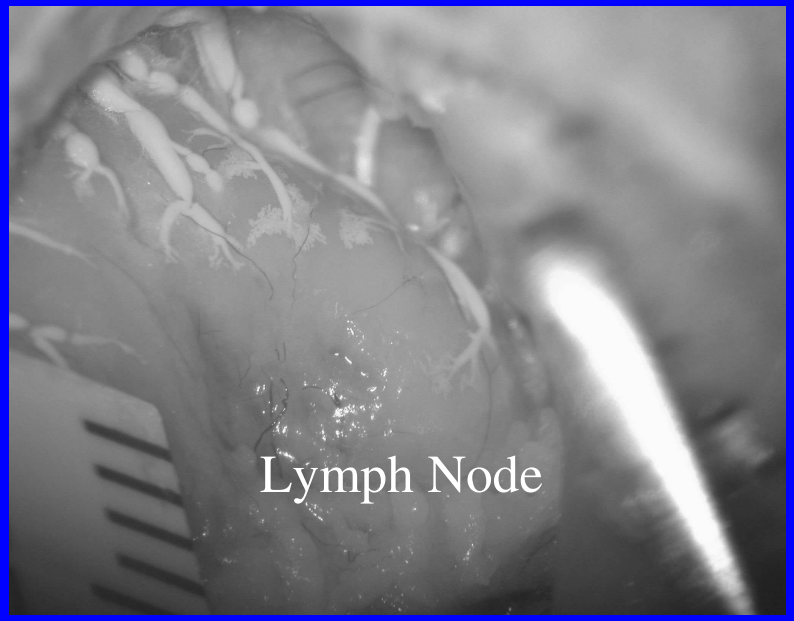


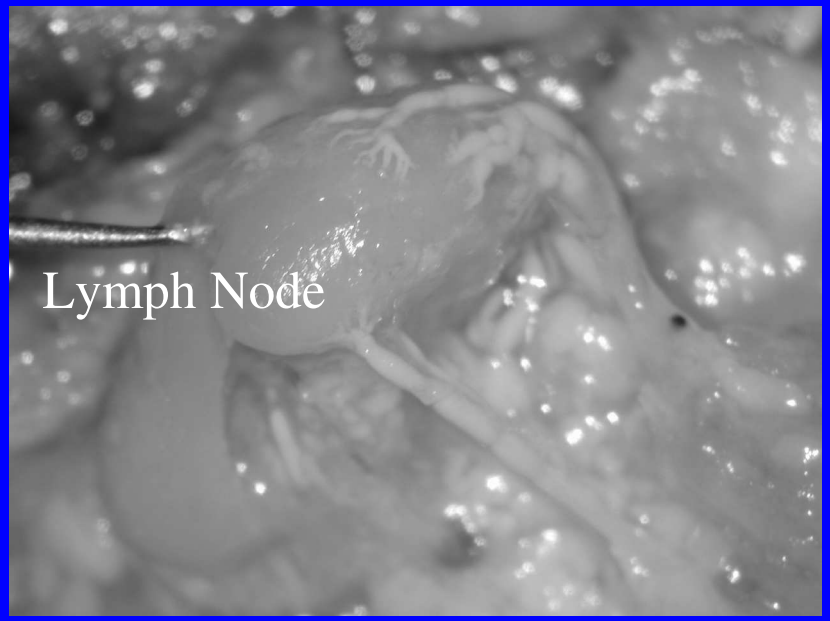
Paranasal lymphatics convey CSF to the retropharyngeal and cervical lymph nodes





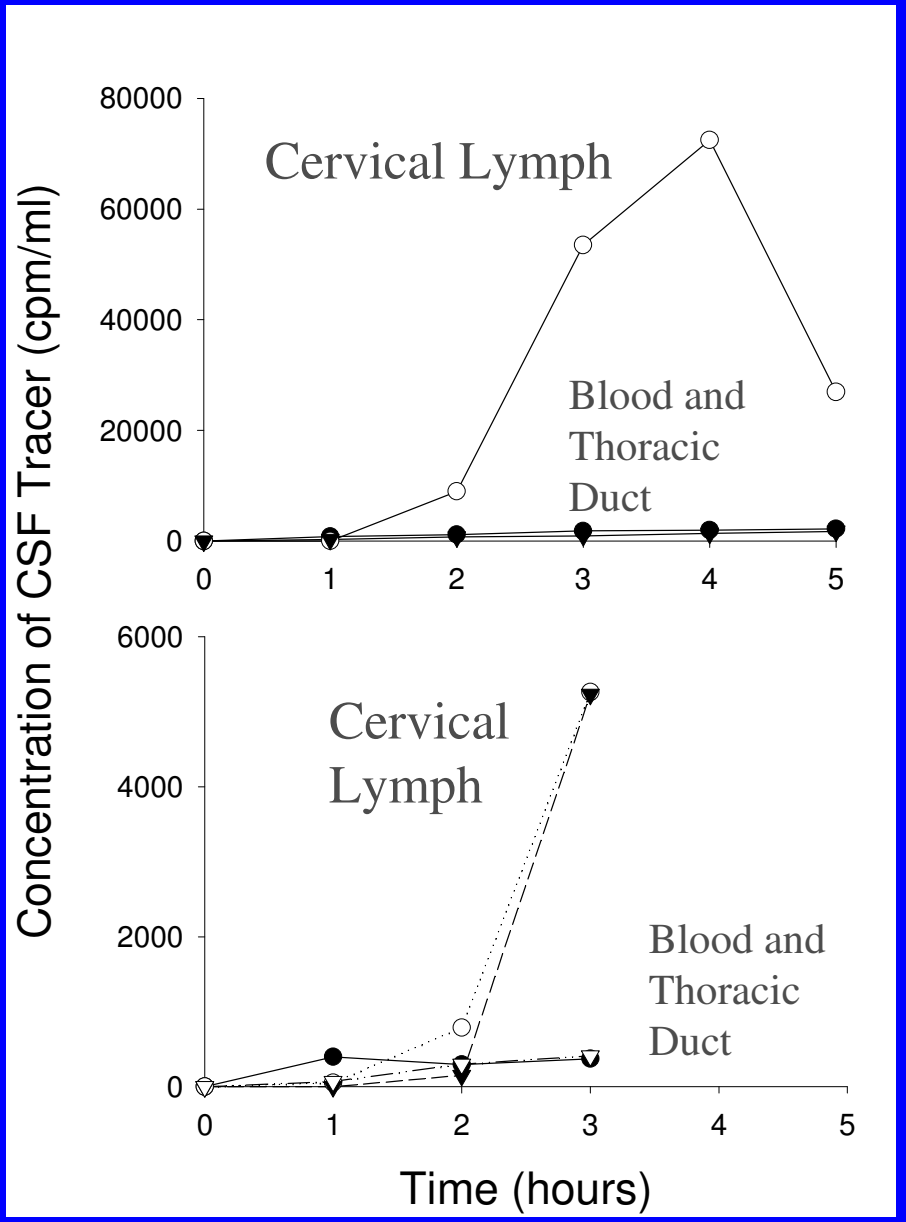
Lymphatic vessels afferent to retro-pharyngeal node containing Microfil



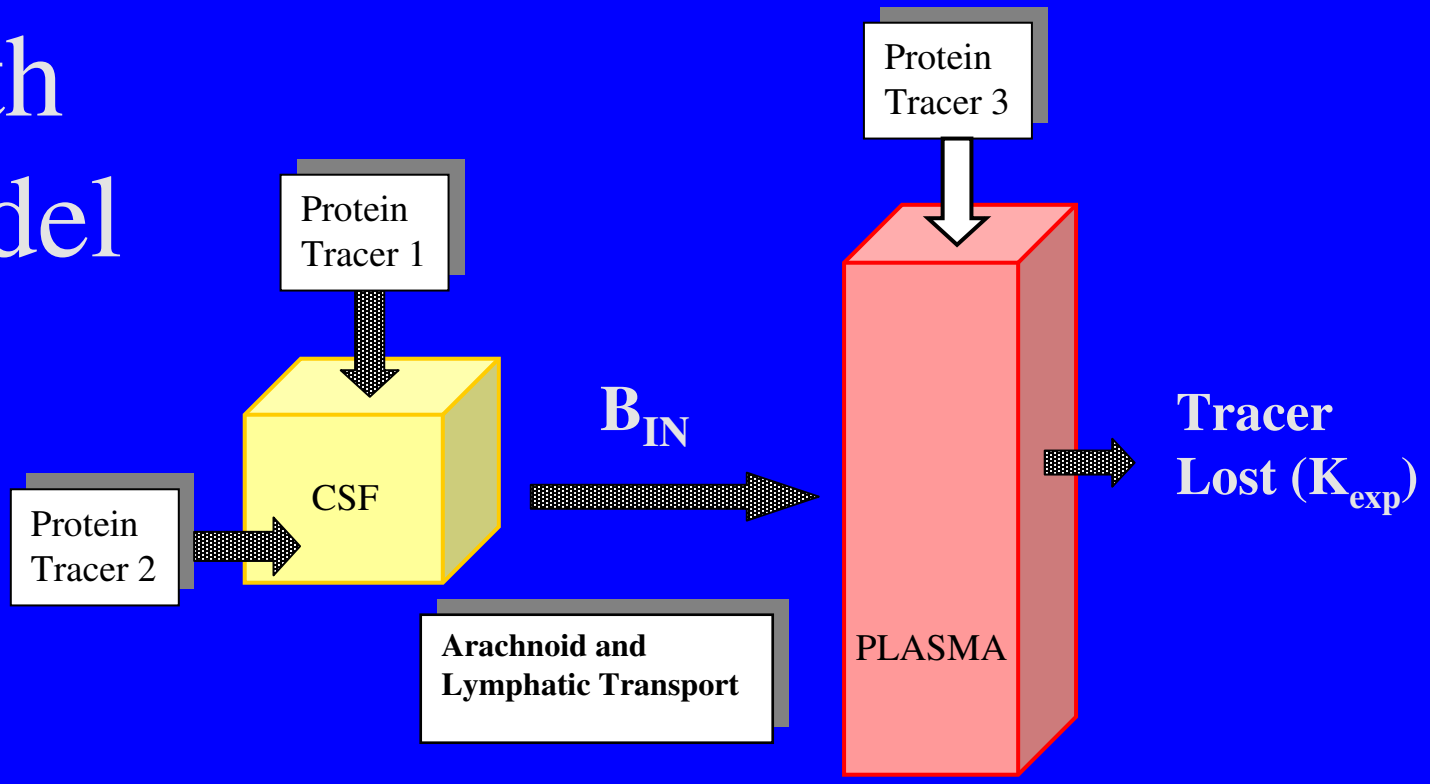


CSF from anterior turbinates transports to the preauricular and submandibular nodes

CSF Transport to Cervical Lymphatic Vessels in the Fetus

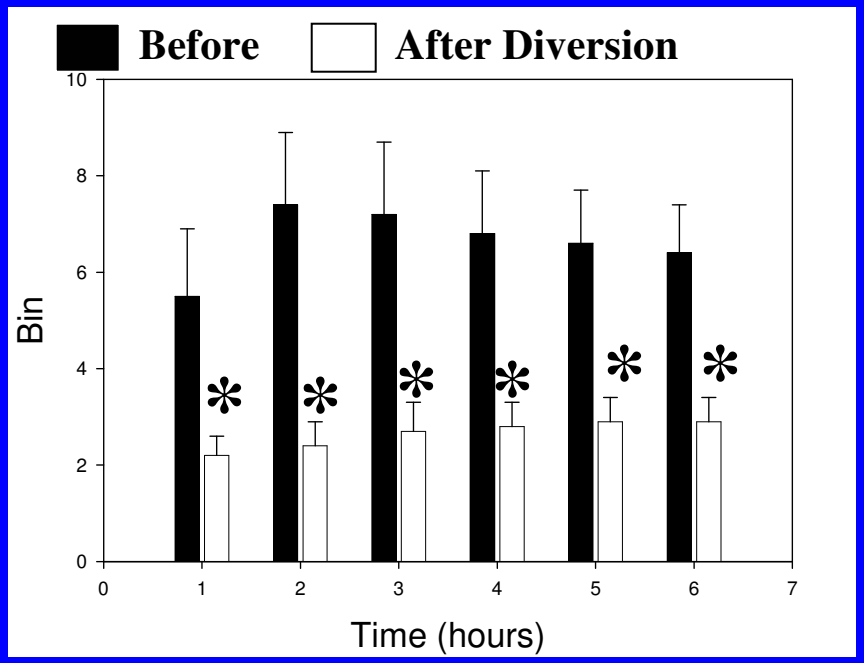


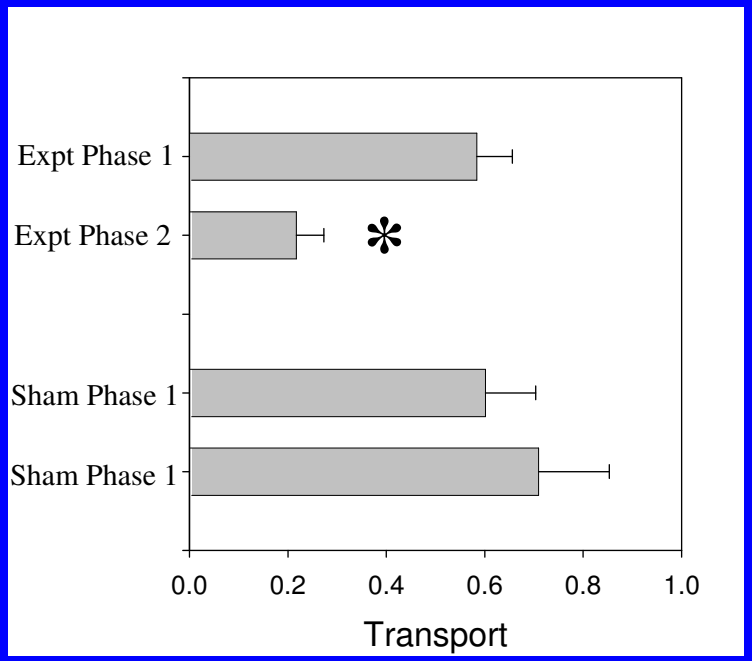
Math Model



$$B^n = \frac{\left[C^P(t^f)\exp(K_{exp}t^f) - C^P(t=0)\right](K_{exp}V^P)}{\exp(K_{exp}t^f) - 1}$$

Effect of Cervical Lymphatic Diversion on the Transport of a CSF Tracer to Plasma



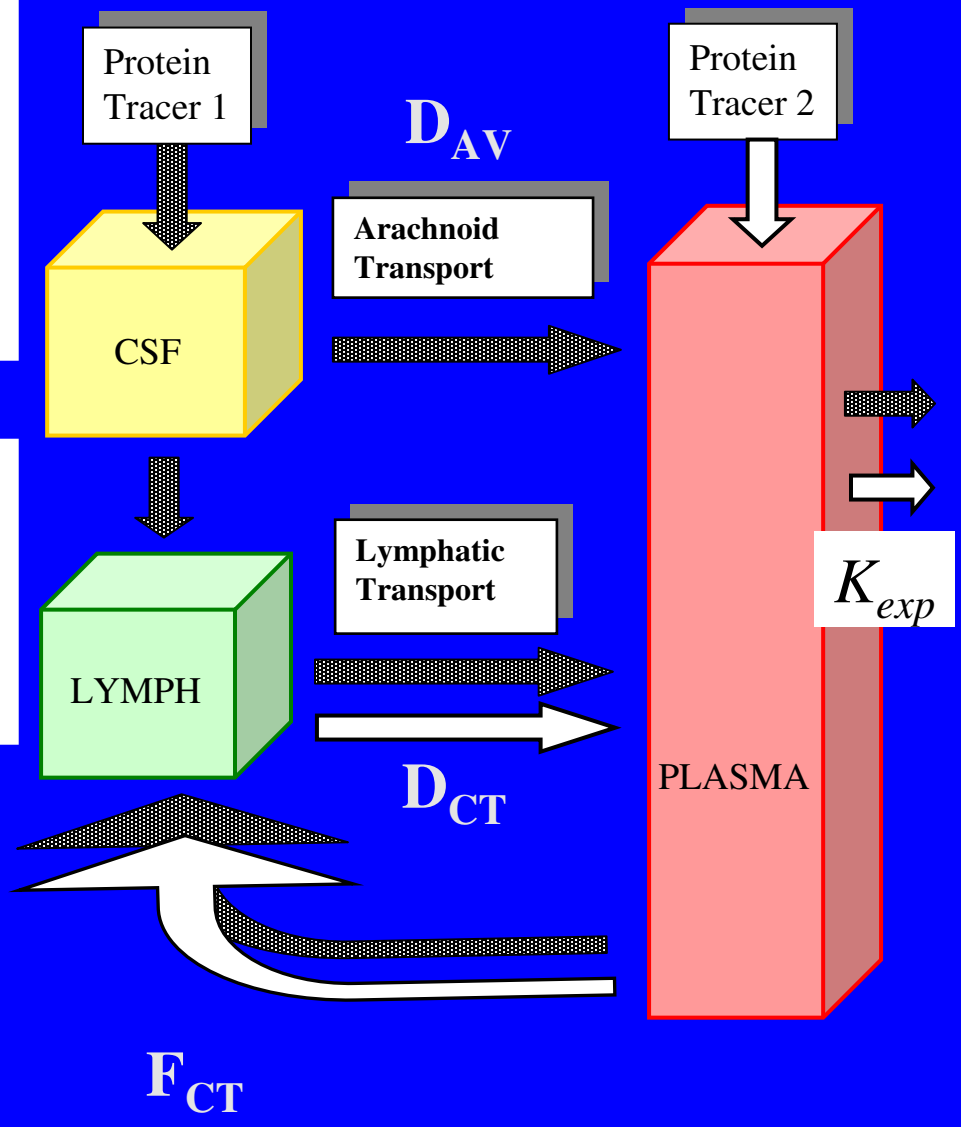


Sheep **Rats**

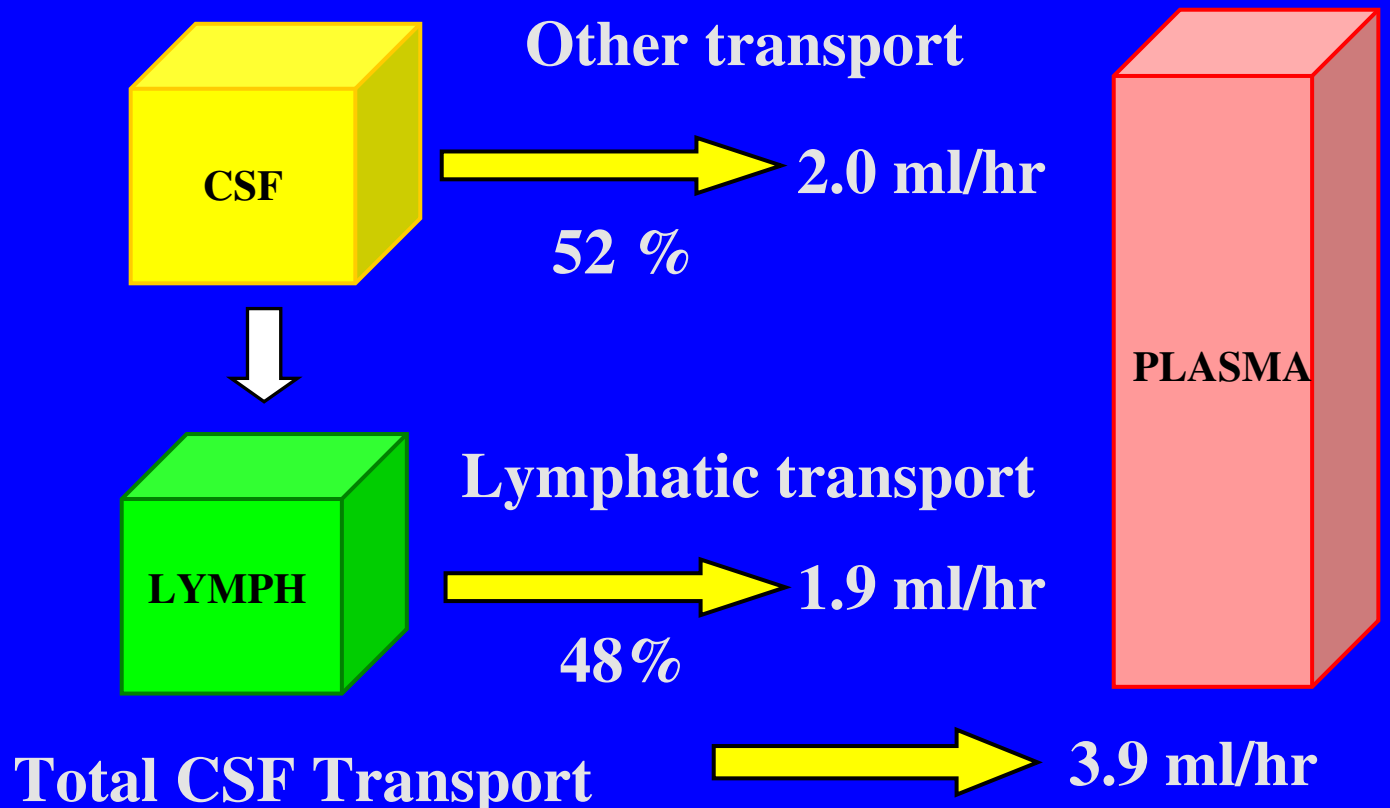
$$D_{AV} = \left[\frac{C_P^{125}(t_f) e^{K_{\exp} t_f} - C_P^{125}(0)}{\int_0^{t_f} \frac{C_{SA}^{125}(t)}{V_P} e^{K_{\exp} t} \, dt} \right]$$

$$D_{CT} = \frac{\int_o^t \left(L_{CT} C_{CT}^{125}(t) - F_{CT} C_P^{125}(t) \right) dt}{\int_o^t C_{SA}^{125}(t) dt}$$

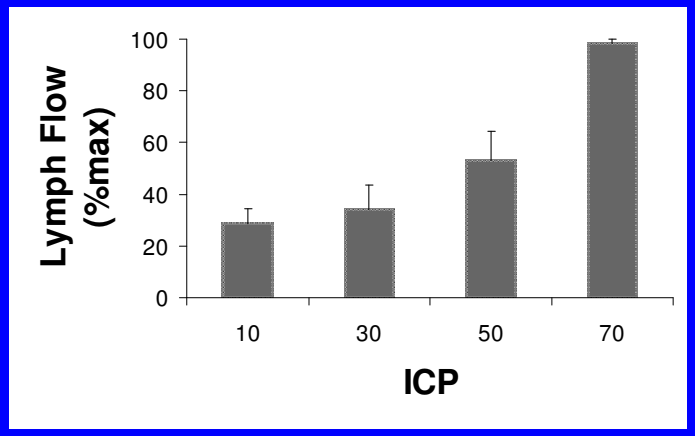
$$F_{CT} = \frac{\int_o^t L_{CT} C_{CT}^{131}(t) \, dt}{\int_o^t C_P^{131}(t) dt}$$



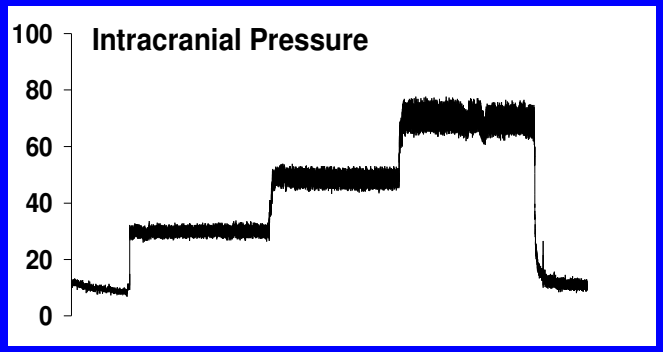
Volumetric cranial CSF Transport in Adult Sheep

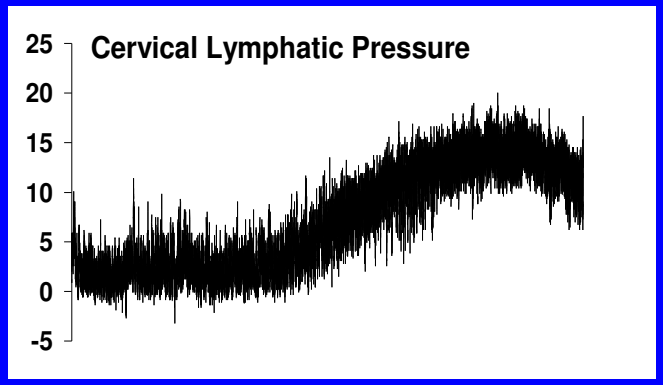


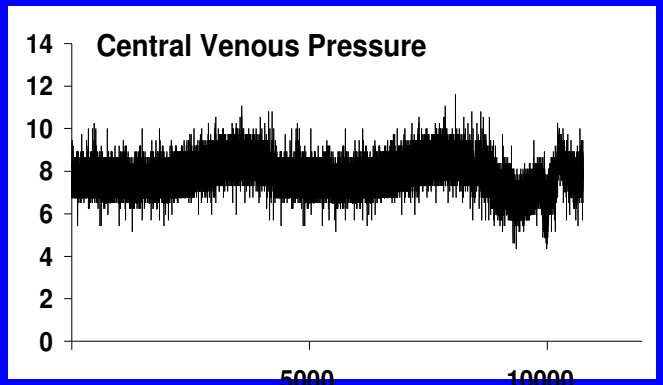
Relationship between ICP and cervical lymphatic Pressure and flow



Intracranial Pressure (cm H2O)



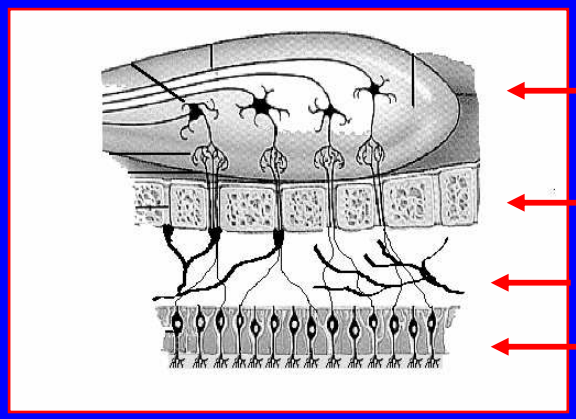




Time (seconds)

Impact of Cribriform Plate on CSF Transport

PHASE 1 → **Same Animal** → **PHASE 2**

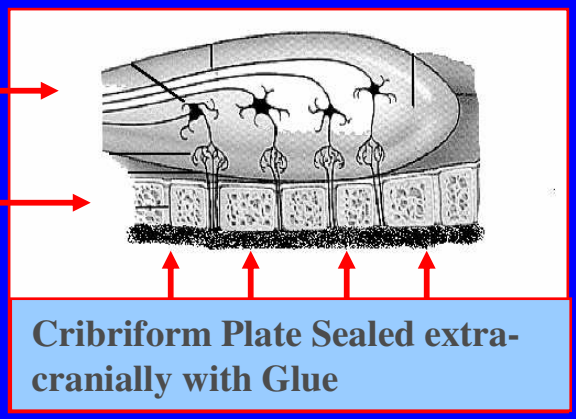


Olfactory Bulb

Cribriform Plate

Lymphatics

Nasal Mucosa

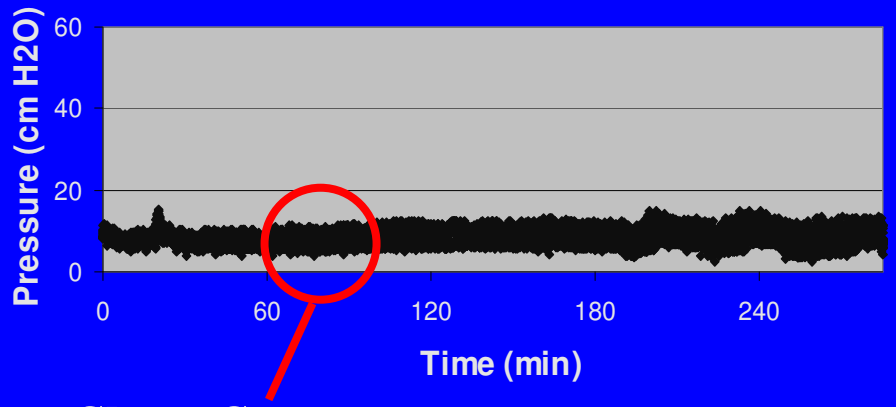


Assessed impact on

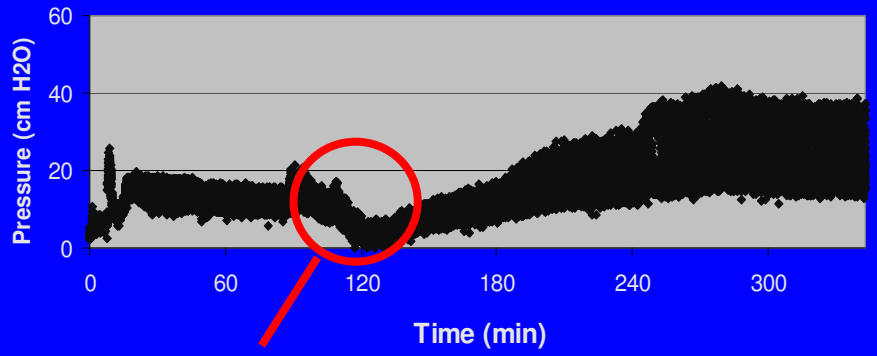
- **(1) Resting intracranial pressure**
- **(2) CSF absorption**
- **(3) CSF outflow resistance**

Impact of Sealing Cribriform Plate on ICP

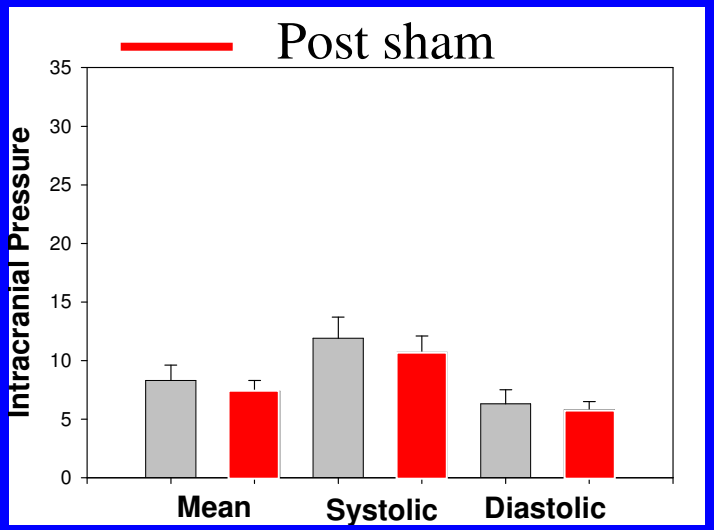
CSF transport into spinal subarachnoid compartment prevented

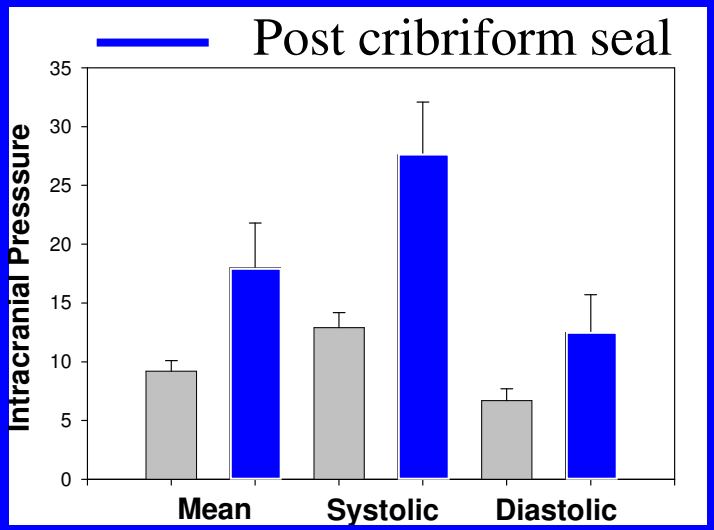


Sham Surgery

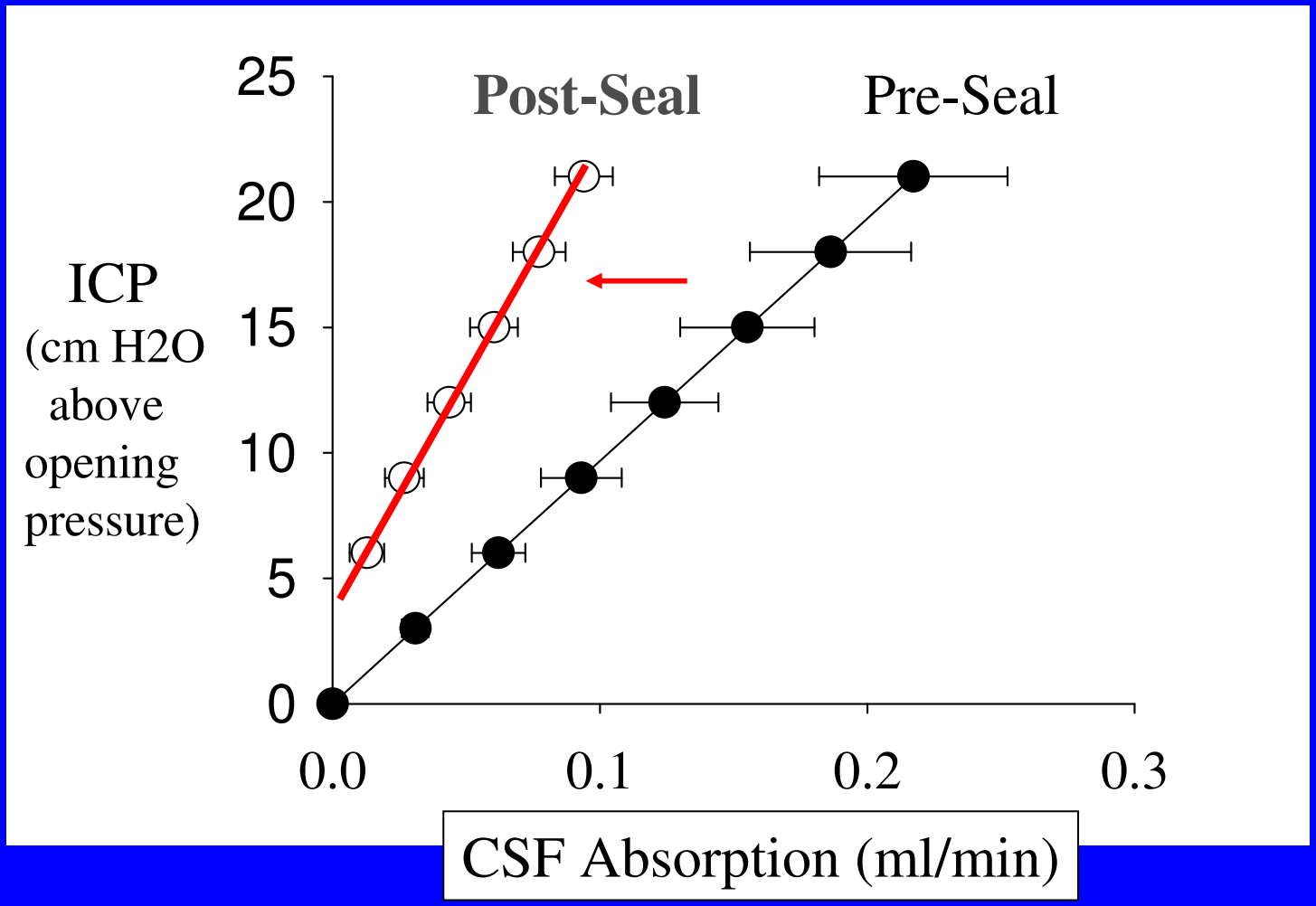


Cribriform Plate scraped and sealed



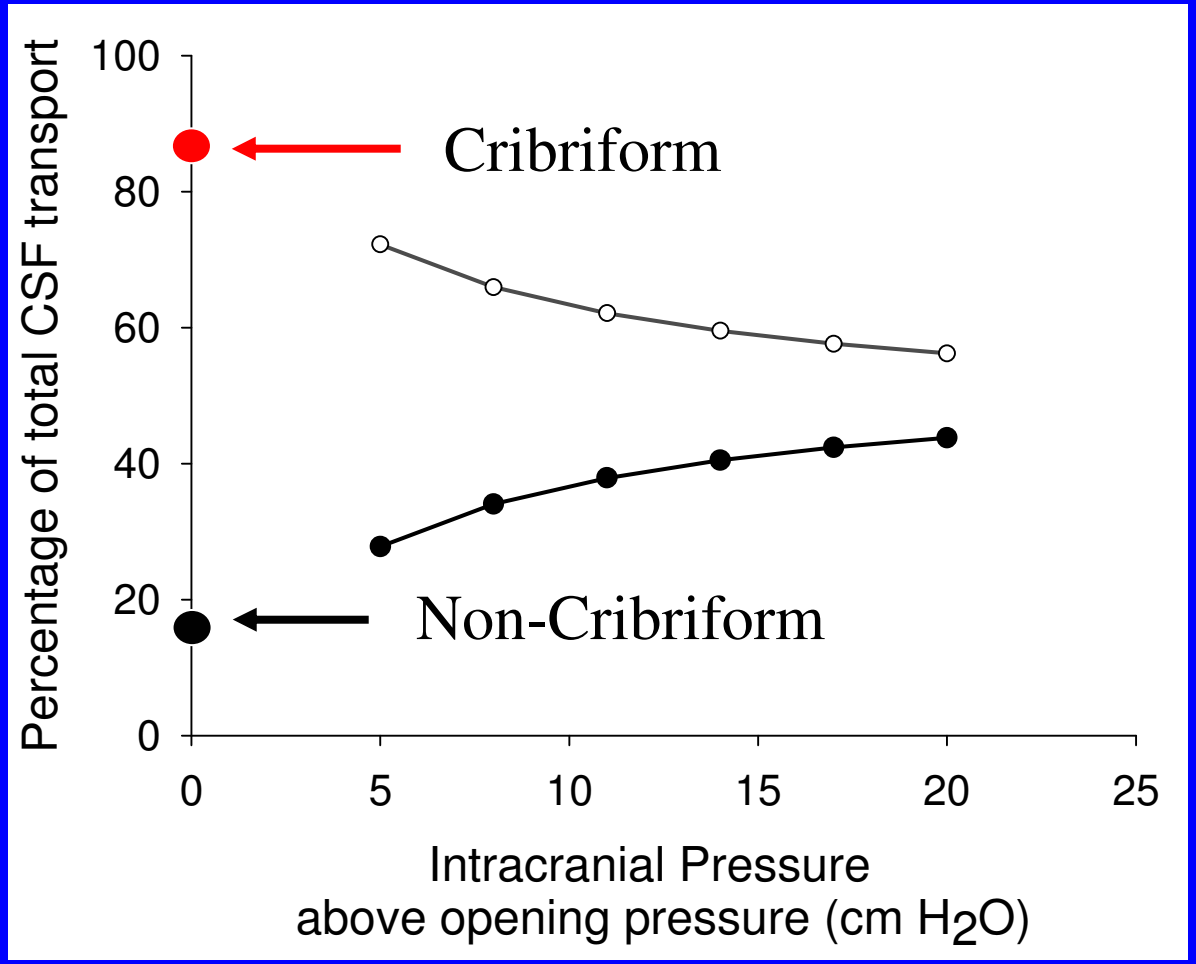


Impact of cribriform plate obstruction on cranial CSF absorption in newborn lambs

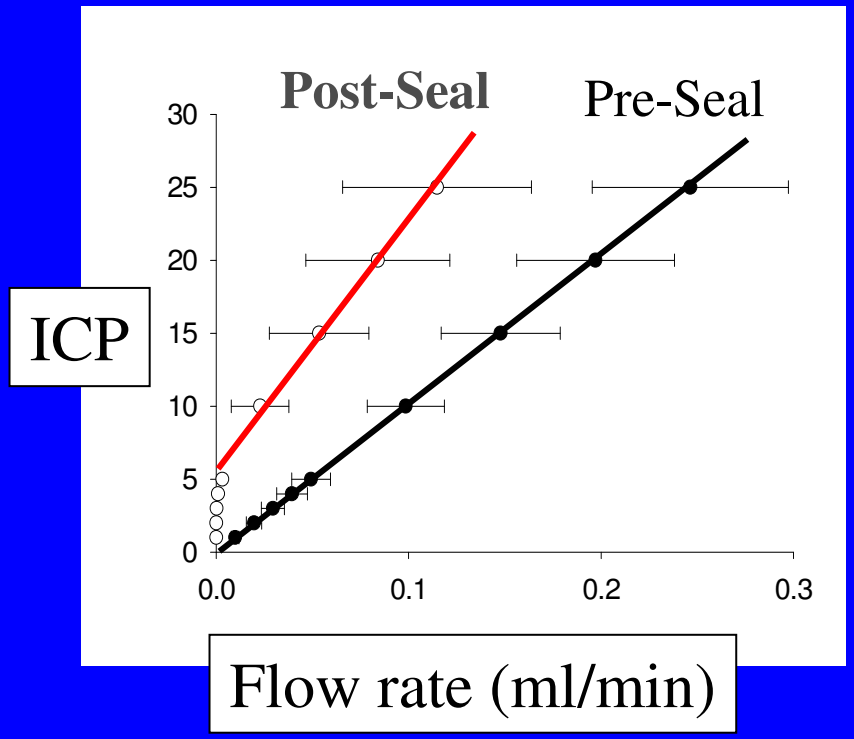


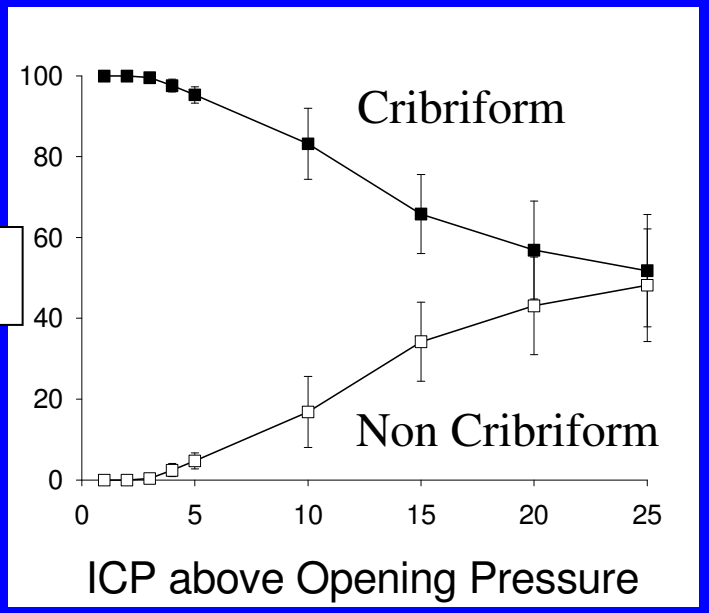
Proportion of cranial CSF transport through cribriform plate in the newborn lamb

Non-cribriform transport: Other lymphatics or arachnoid projections?

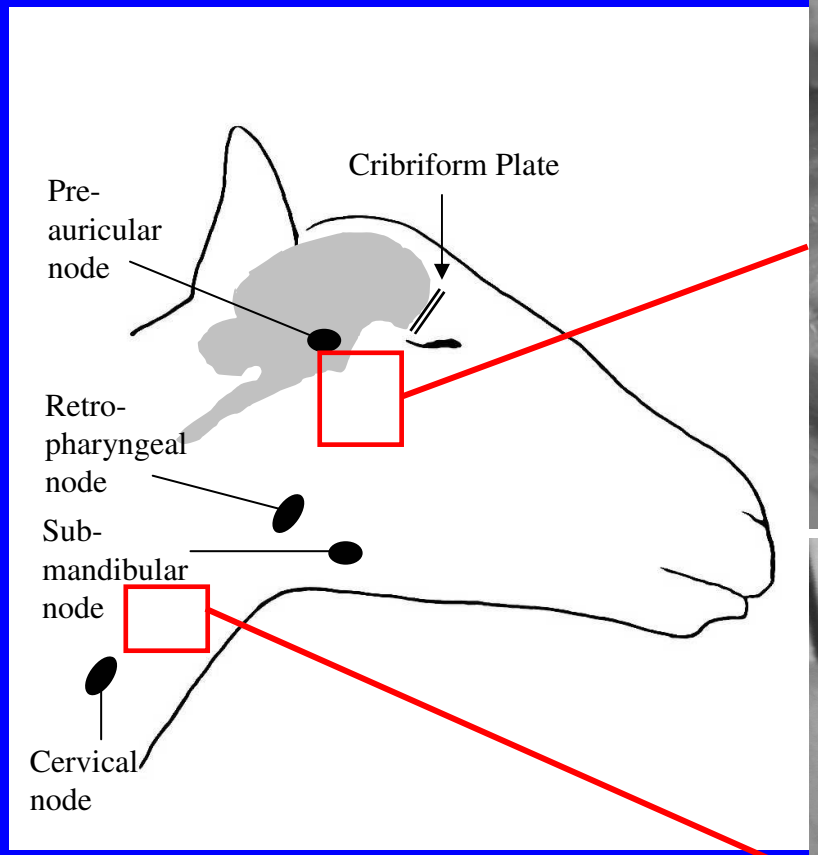


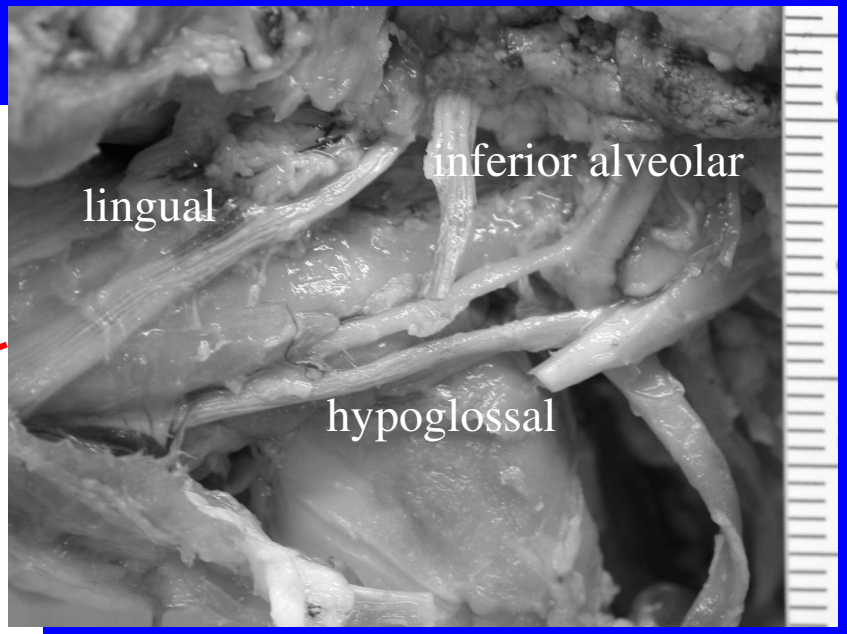
Impact of Sealing Cribriform plate on cranial CSF transport in the adult sheep

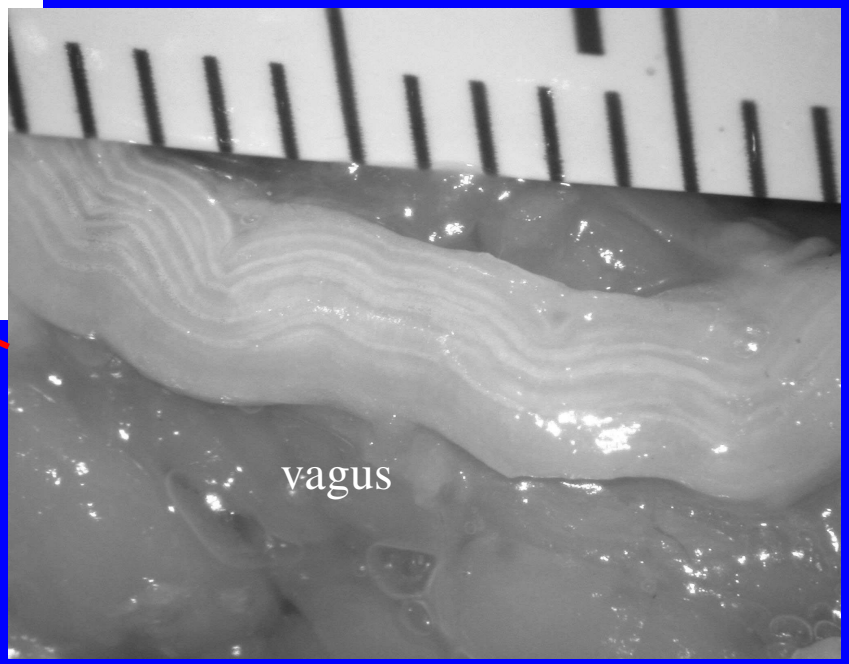




Proportion of cranial transport through Cribriform Plate

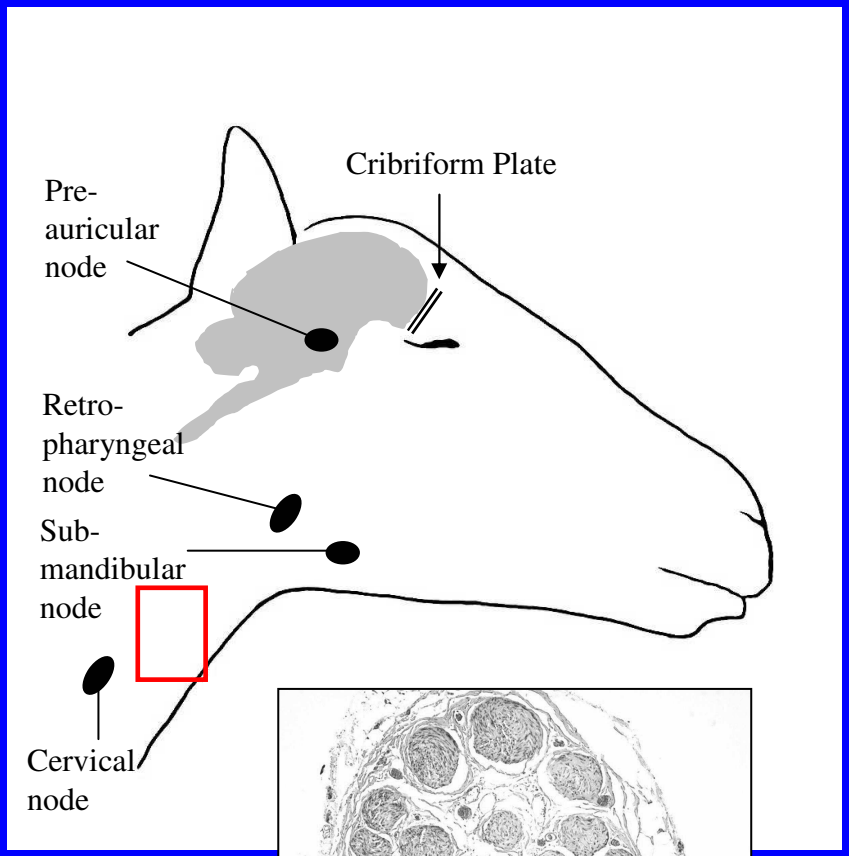


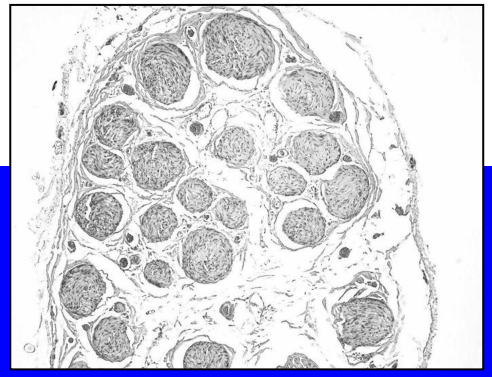




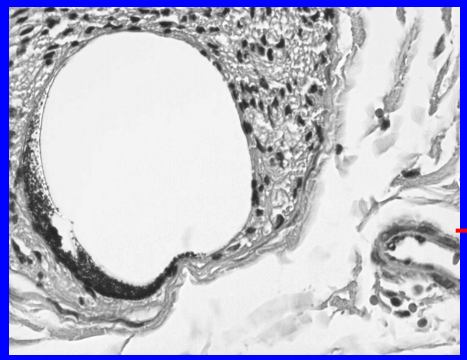
Cranial Nerves

Vagus Nerve





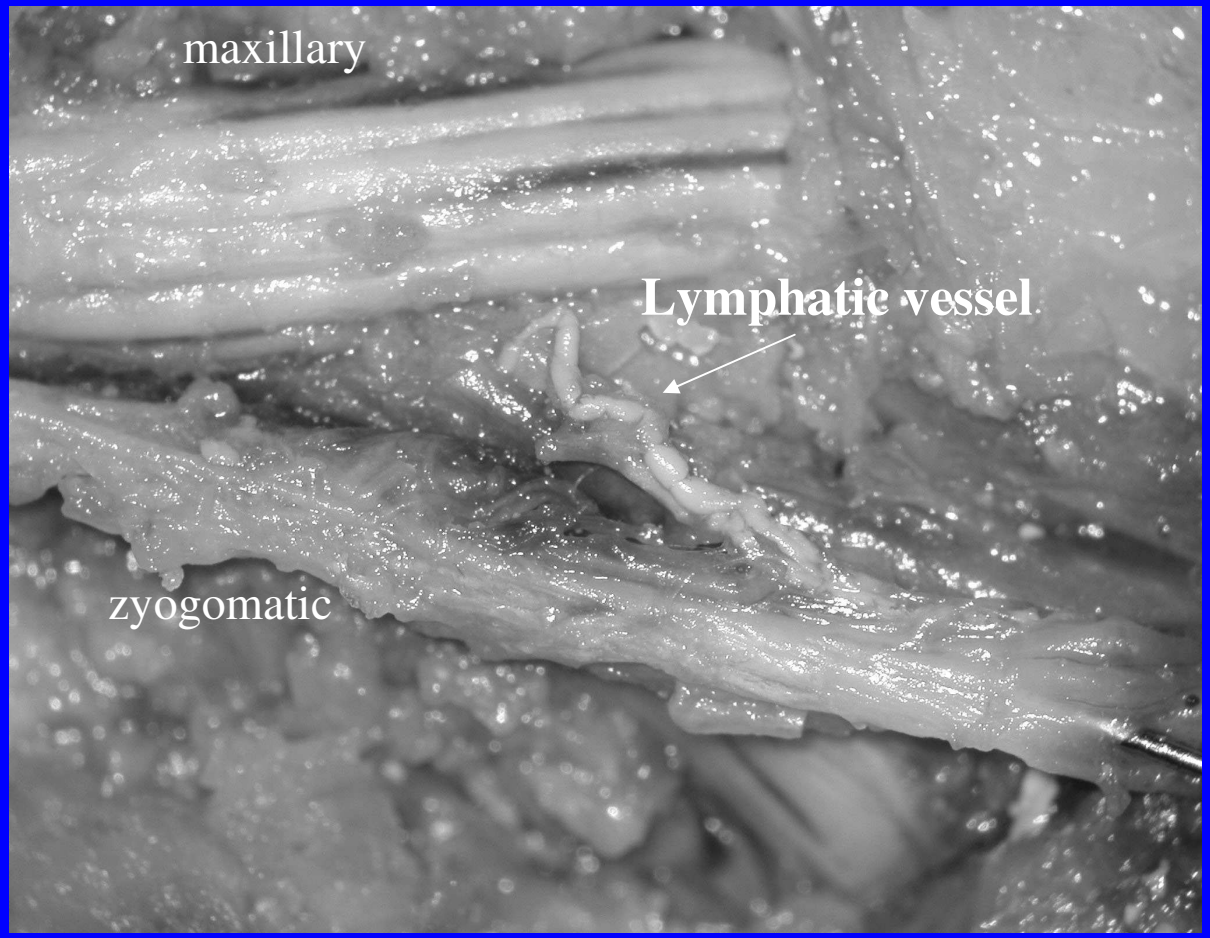
control



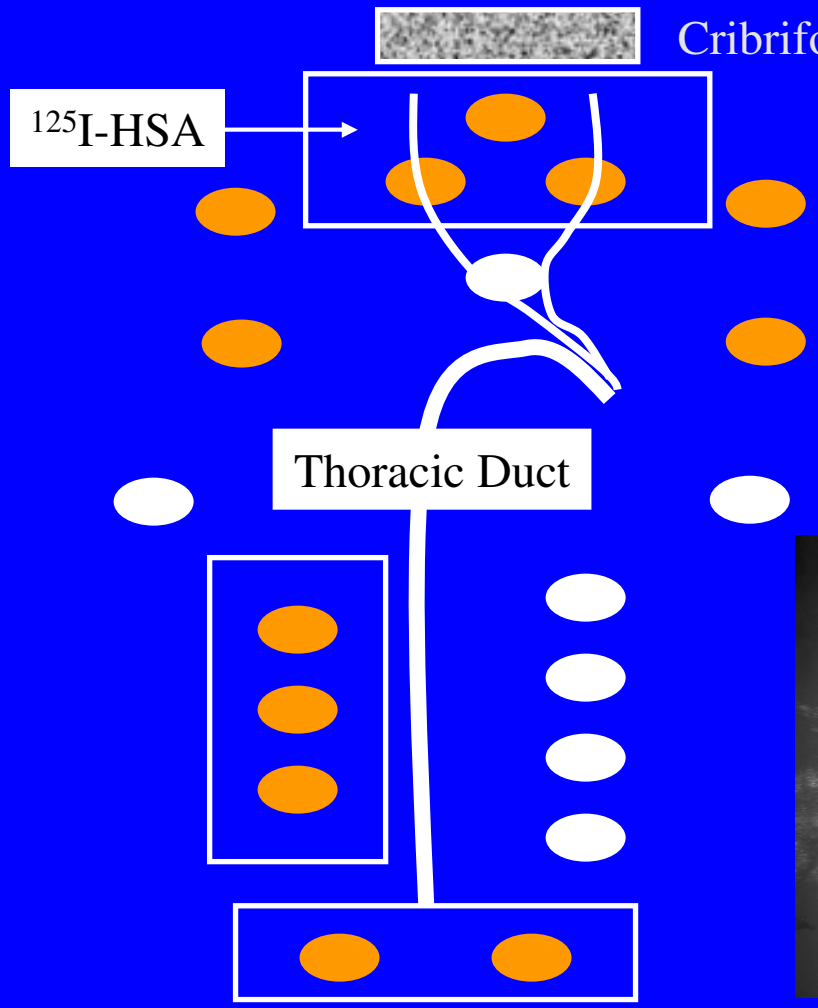
+ Microfil

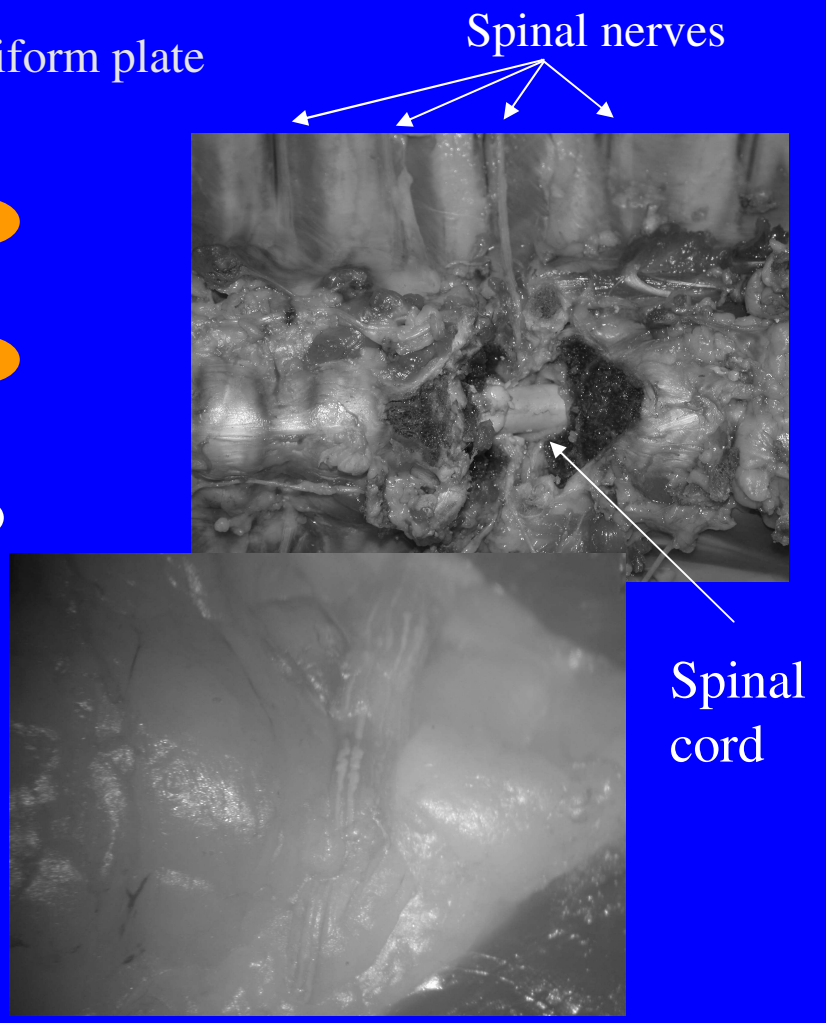
Microfil present in subperineurial space
or within endoneurium

Endoneurial spaces provide a linkage between CSF and lymphatic vessels

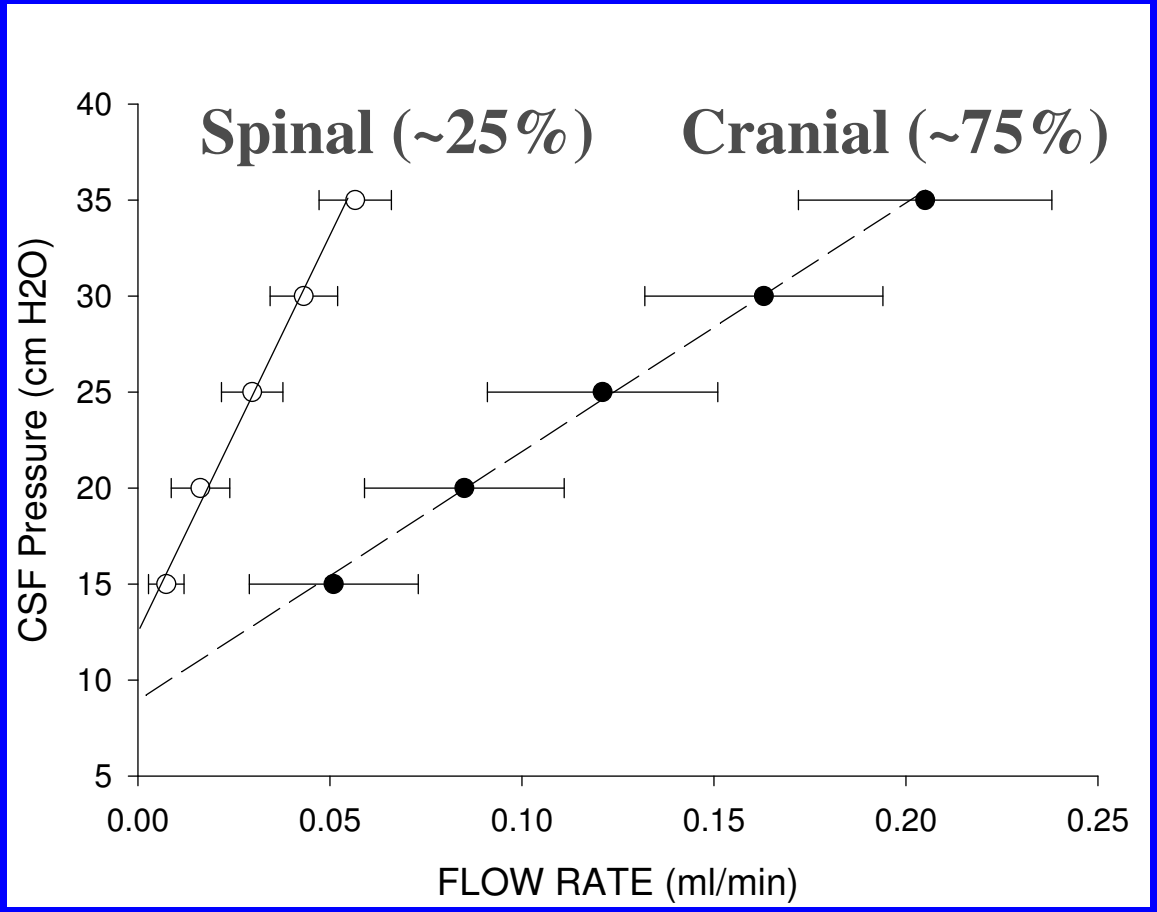


CSF transport along cranial and spinal nerves



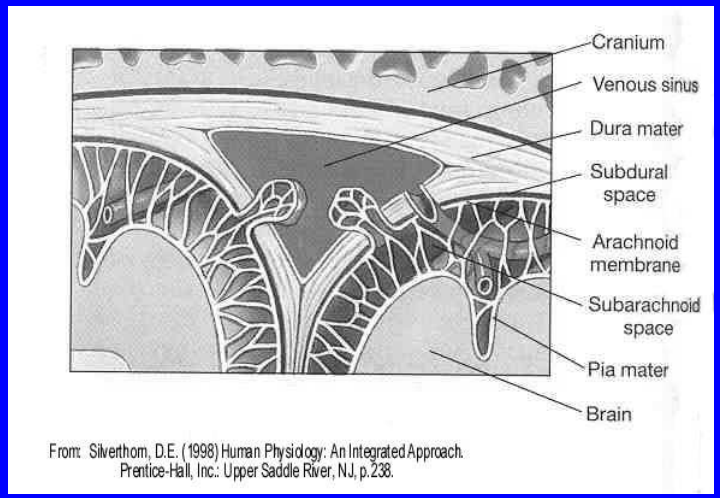


Cranial and Spinal CSF Conductance

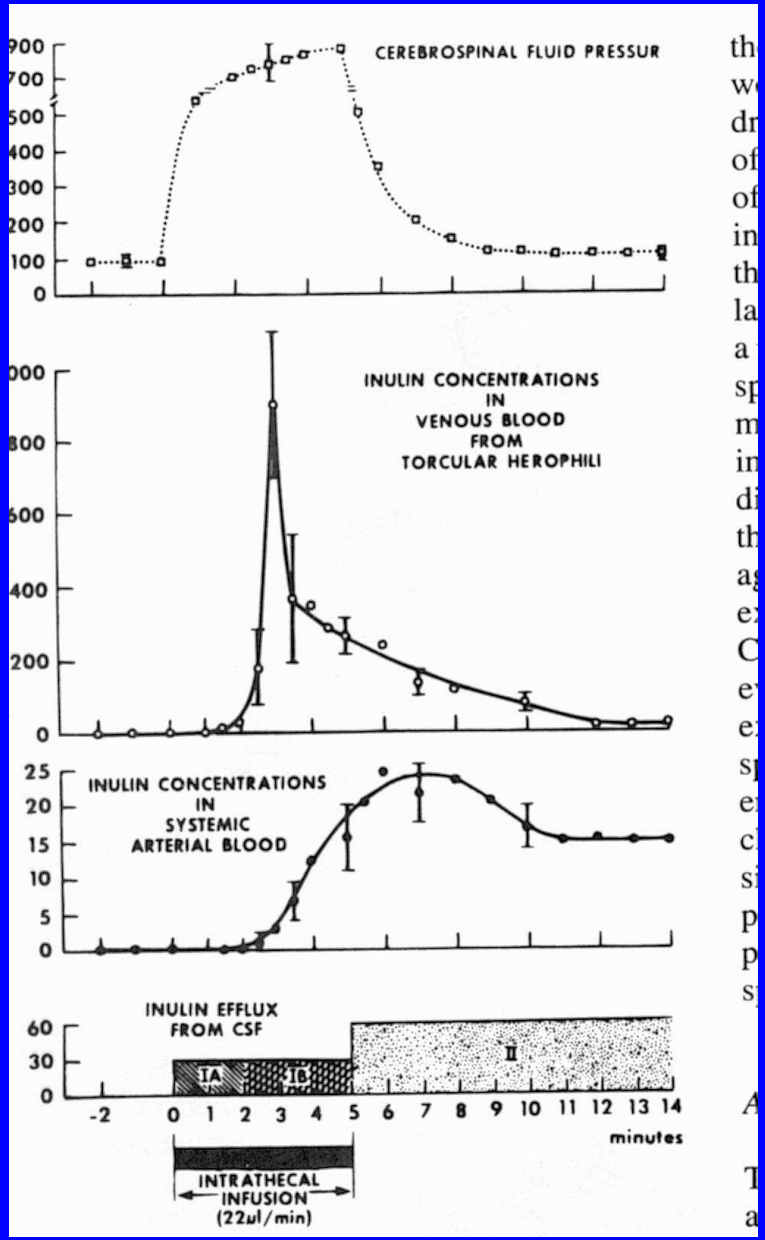


Arachnoid Projections- attempts to quantify

Mann et al., J. Neurosurg. 50: 343-348 →

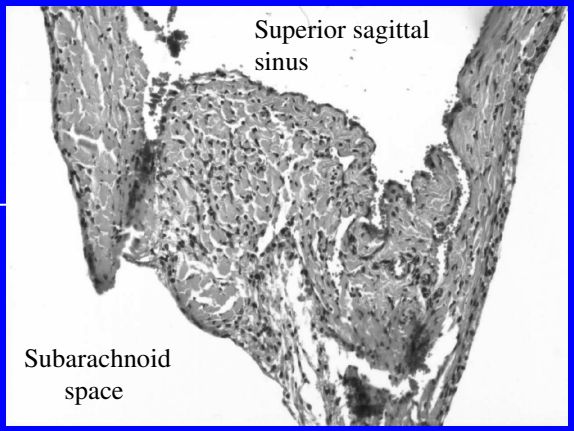


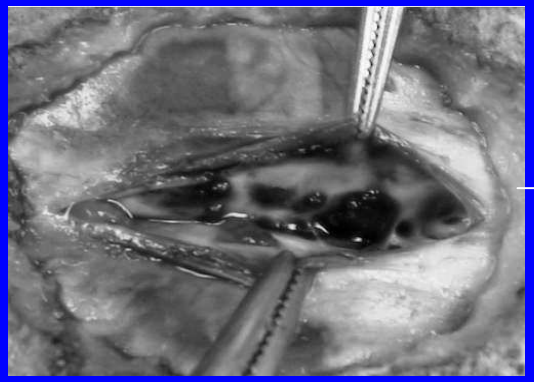
From: Silverthorn, D.E. (1998) Human Physiology: An Integrated Approach. Prentice-Hall, Inc.: Upper Saddle River, NJ, p. 238.



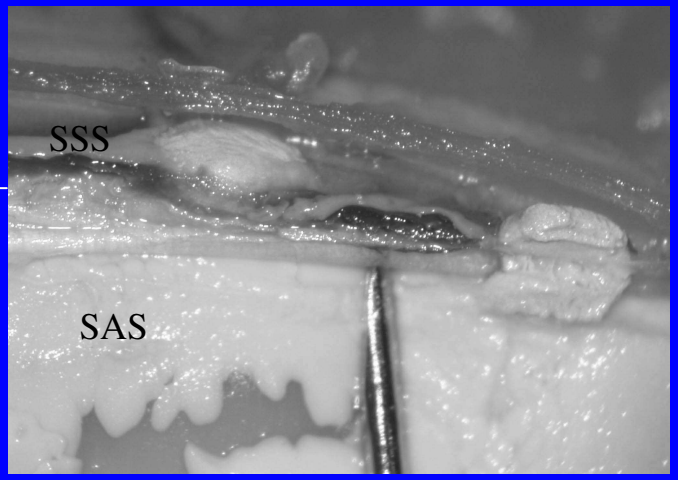
“Classical” pathway: arachnoid projections

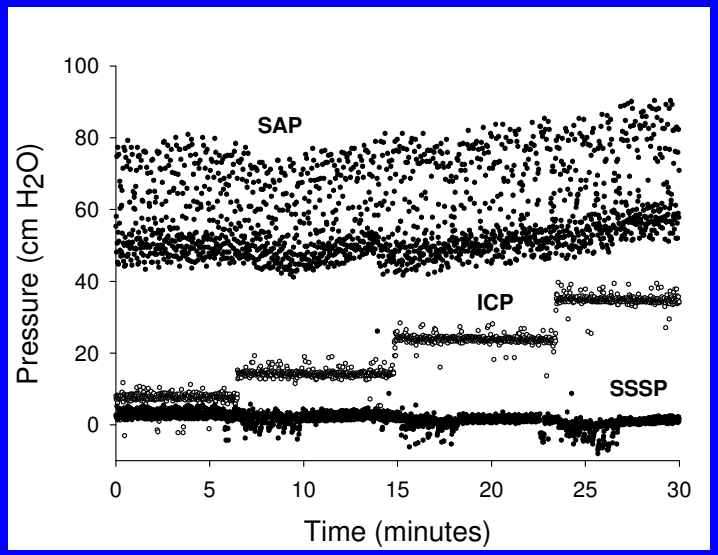
Neonate

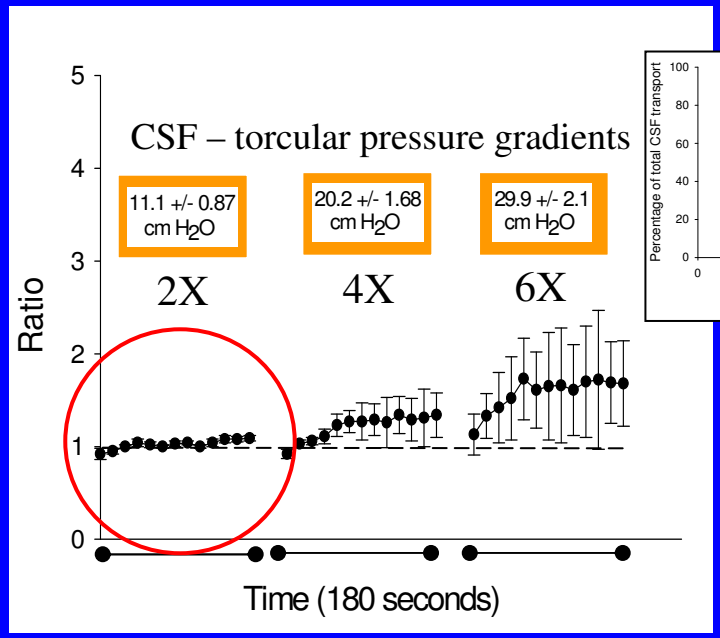


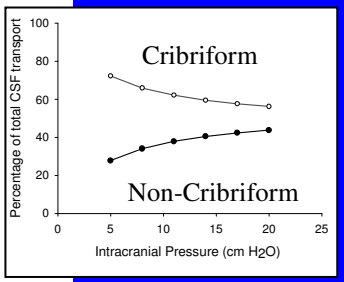


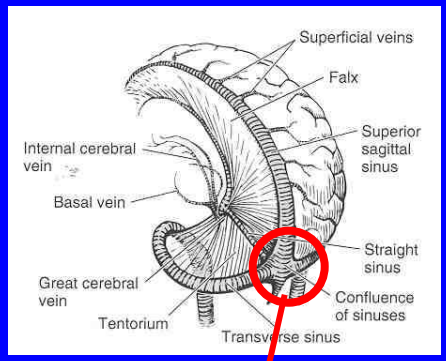
Adult











CSF Tracer

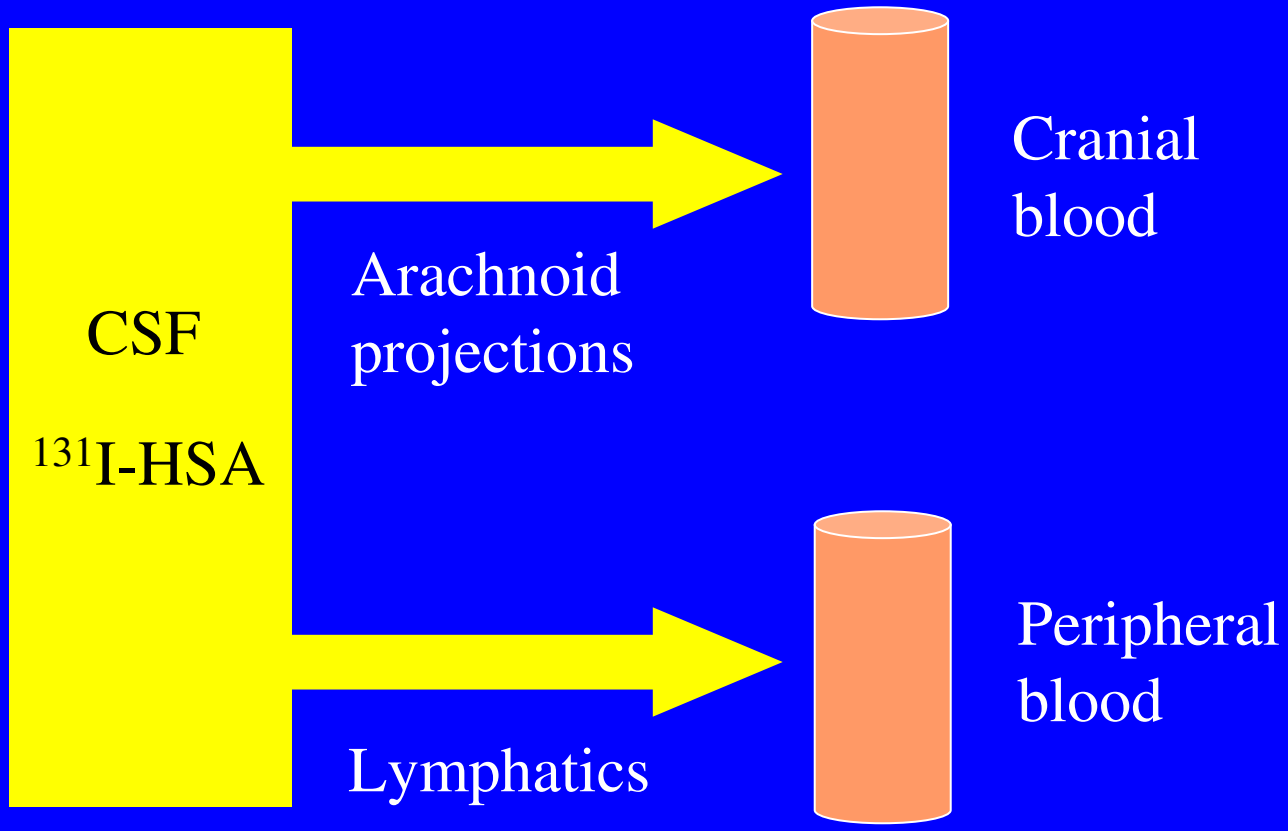
CSF

Cranium

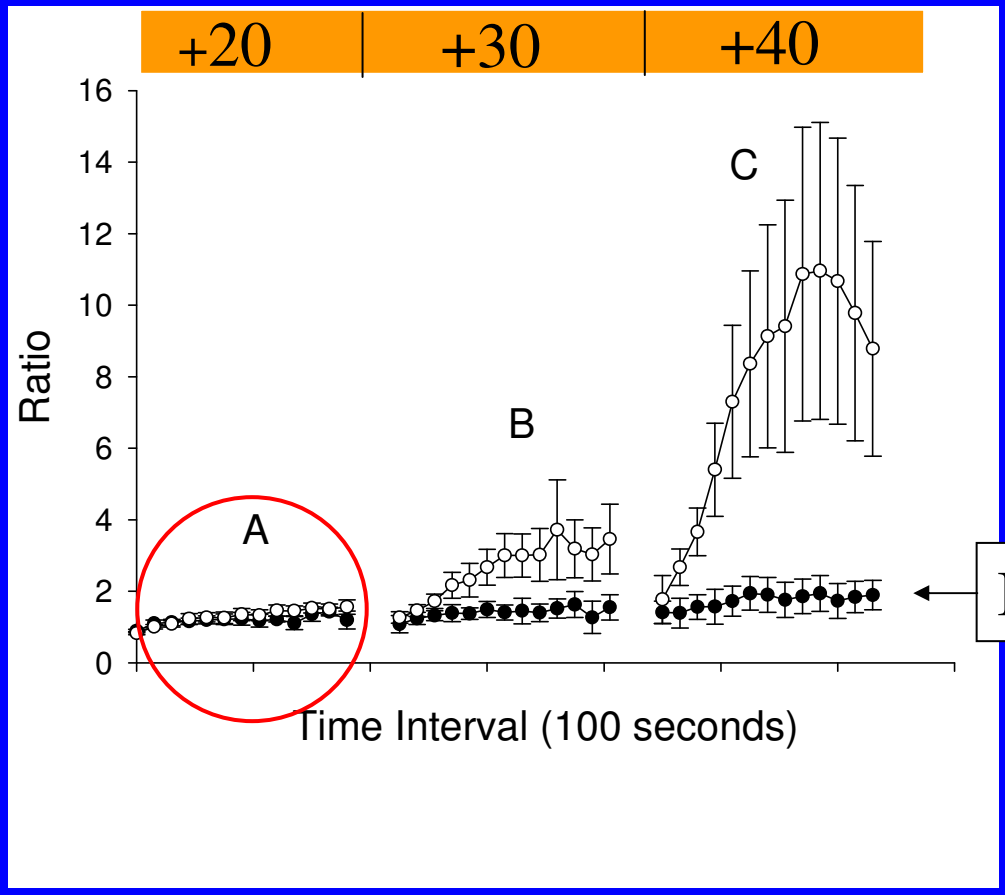
Venous System

Neonate

Potential problems with this approach



Transport into cranial venous system-Adult

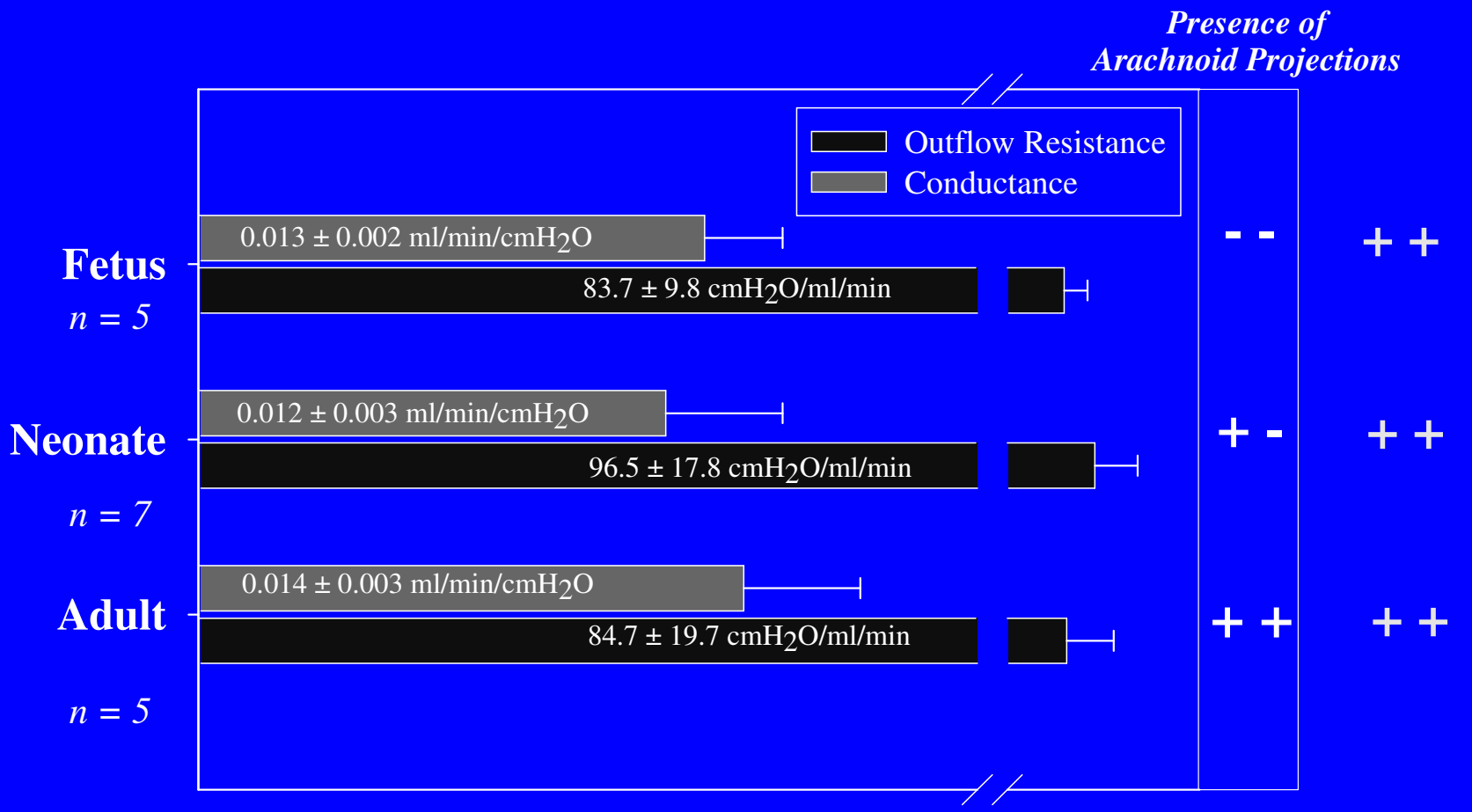


Arachnoid projections … high pressure relief valves ?

Intact

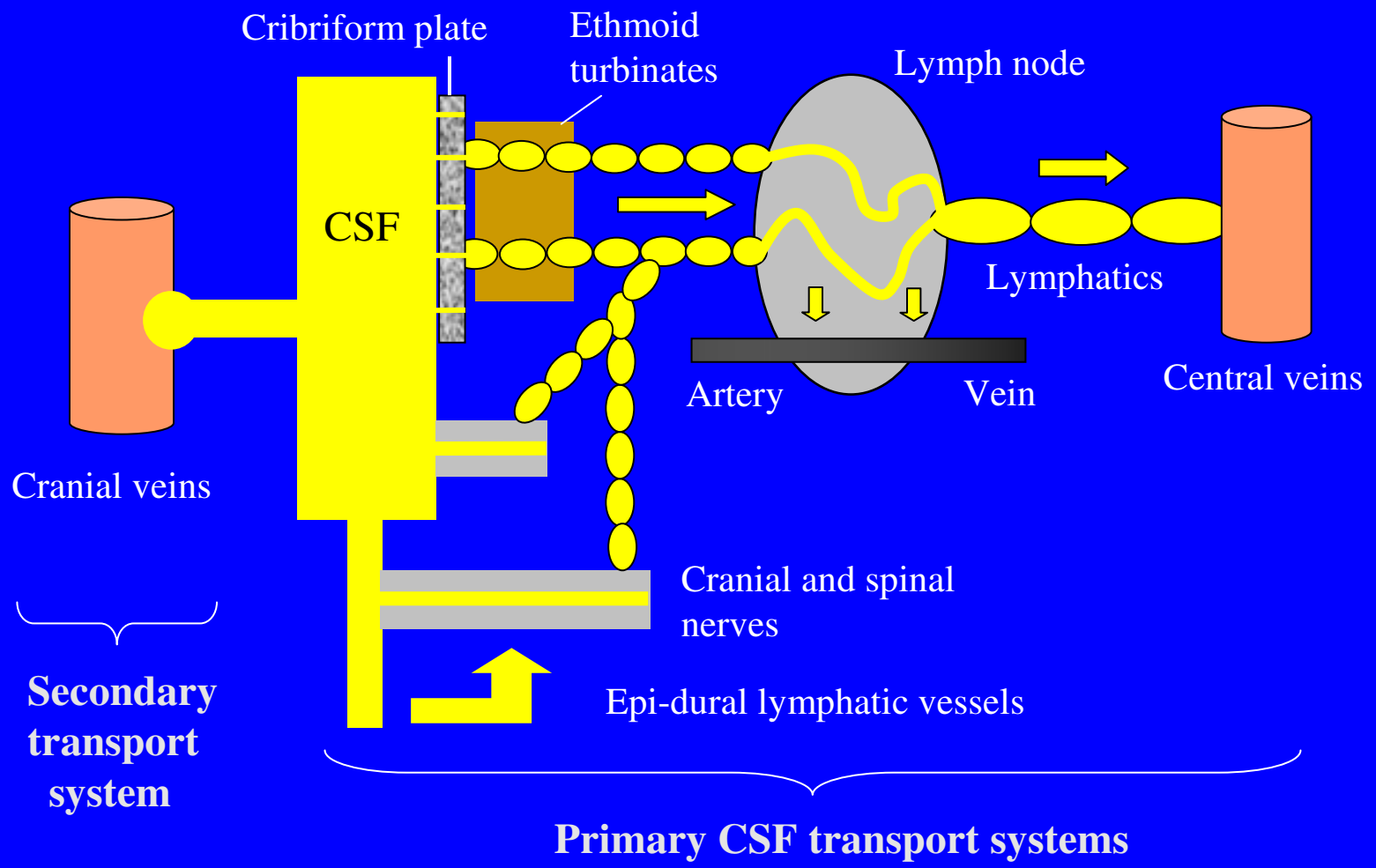
CSF absorption through cribriform plate blocked and transport into spinal subarachnoid space prevented

Global CSF Transport Characteristics in sheep

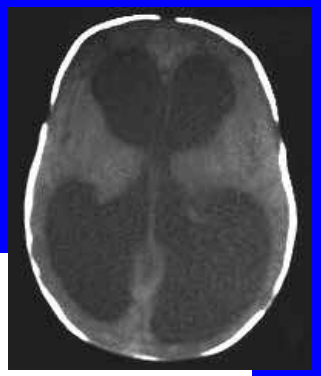


Lymphatics

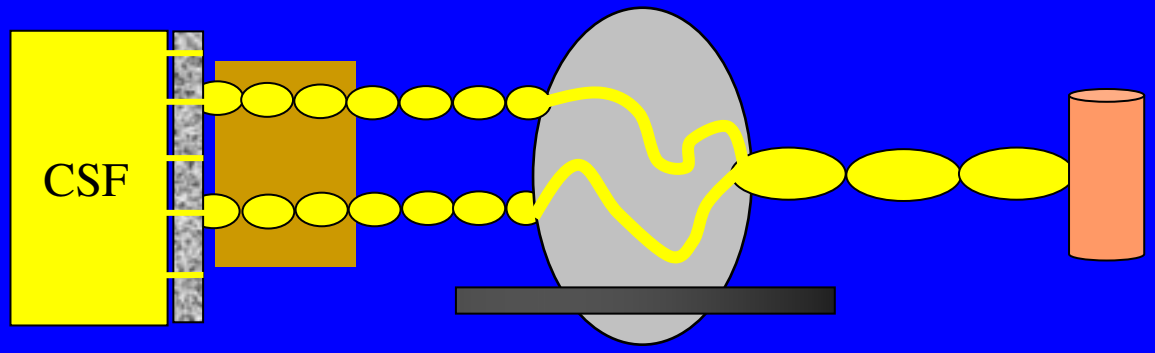
Lymphatic CSF 'transport systems': the primary CSF absorption pathways



Where do we go from here ?



-studies in humans (Microfil)
-can CSF transport into lymphatics be impaired ?
-does interference with lymphatic pathways lead to a transmantle pressure gradient and hydrocephalus ?



Human cribriform plate →

Kalmey et al., (1998), Anat. Rec. 251: 326-329

Contributors to Project

D. Armstrong
M. Boulton
R. Bosanovic-Socic
R. Elias
P. Li
R. Mollanji
C. Papaiconomou
I. Silver
A. Zakharov

N. Azizi
J. Djenic
C. Kim
L. Koh
L. Makarian
R. Mohamed

M. Flessner
J. Hay
R. Midha
M. Katic
J. P. Szalai