Fluid balance in the Brain: A Perspective

Roy O. Weller, MD PhD. Cheryl A Hawkes, PhD.
Roxana O. Carare MD PhD.

University of Southampton UK (row@soton.ac.uk)



Extracellular Fluids of the brain

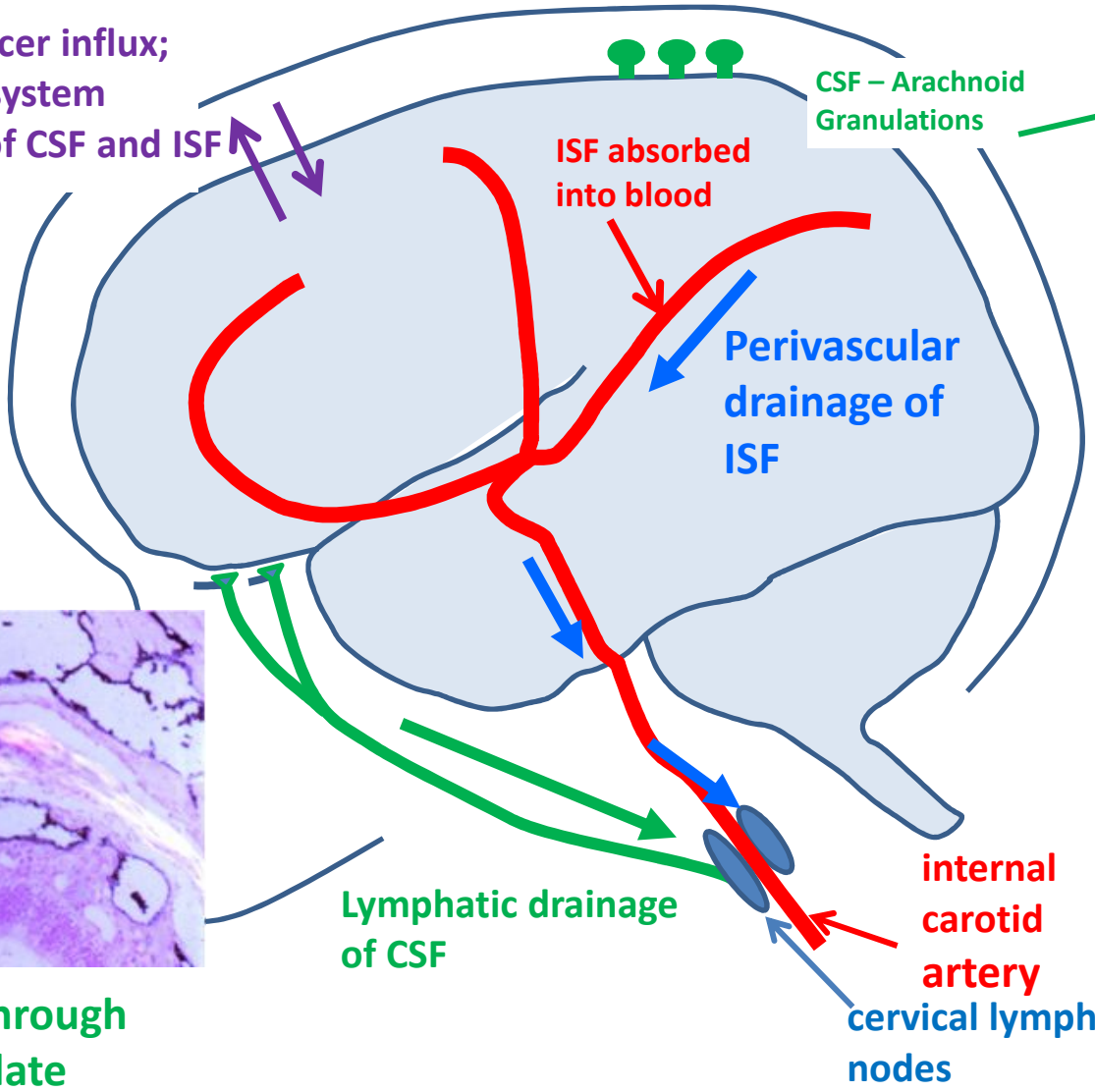
- Blood
- Cerebrospinal fluid (CSF) in the ventricles and subarachnoid space
- Interstitial fluid (ISF) within the parenchyma of the brain and spinal cord

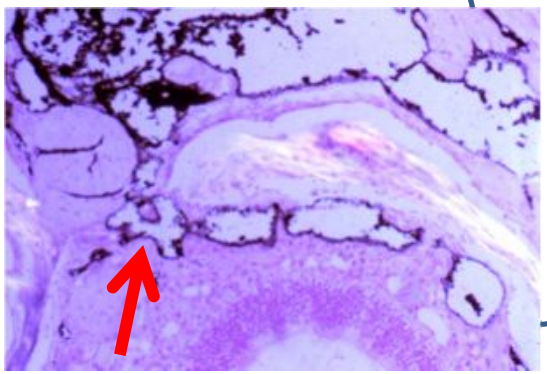
Production and elimination of CSF and ISF are both important for maintaining homoeostasis in the CNS

Review:

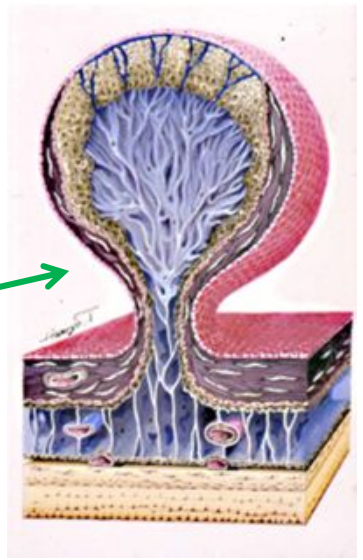
- Elimination pathways for CSF
- Elimination pathways for Interstitial fluid (ISF)
- Interconnections between CSF and ISF
- How pathology helps to define normal functions of fluid drainage pathways and the limitations of those pathways.

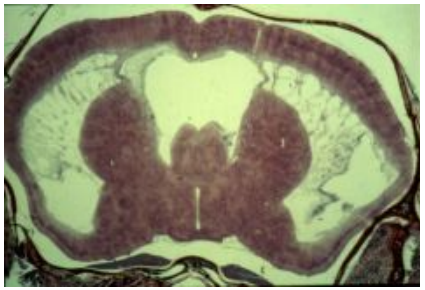
Drainage of CSF and Interstitial Fluid (ISF) from the Brain





CSF drains through cribriform plate





Pathology:
Hydrocephalus: ISF drainage pathways fail to cope

Interstitial fluid and solutes of the brain

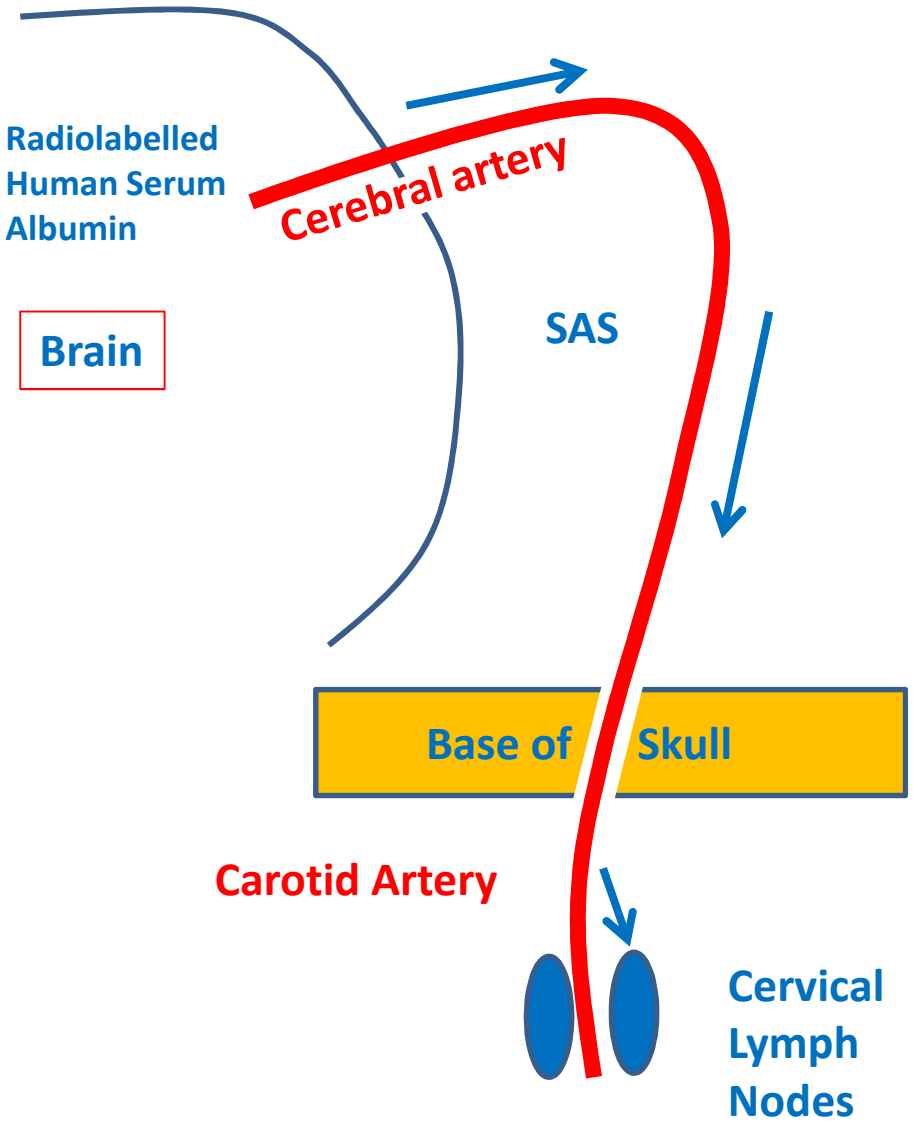
Origin: from blood and from tissue metabolism ***(Abbott et al 2006)***

Elimination of fluid and solutes from the brain

- **Absorption into blood – receptor mediated** ***(Shibata …. Zlokovic et al 2000)***

- **Rapid and Specific perivascular drainage along basement membranes in the walls of cerebral capillaries and arteries to cervical lymph nodes**
  (*Szentistvanyi … Cserr 1984; Carare et al 2008; 2013)*
  - ***A very important system for Neuroimmunology and in the pathology of Alzheimer's disease***

Perivascular Lymphatic Drainage of ISF from the Brain



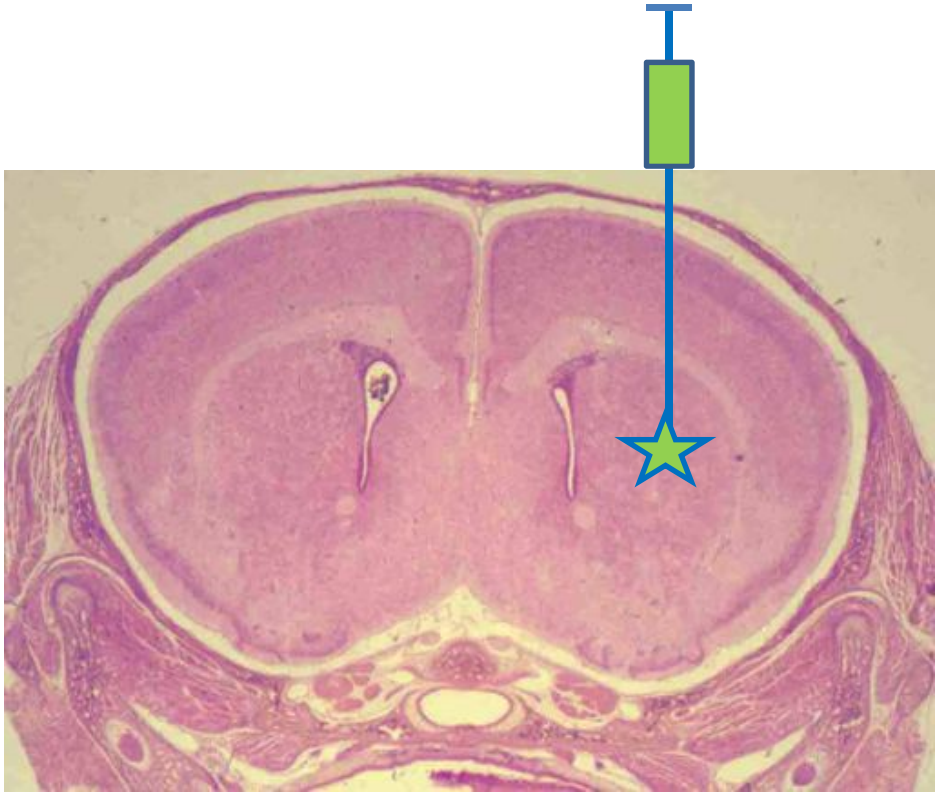
Interstitial Fluid and Solutes drain along the walls of Arteries to Cervical Lymph Nodes

Some 15% of tracer in ISF leaks into CSF

Speed of drainage comparable to Lymphatic drainage in other organs

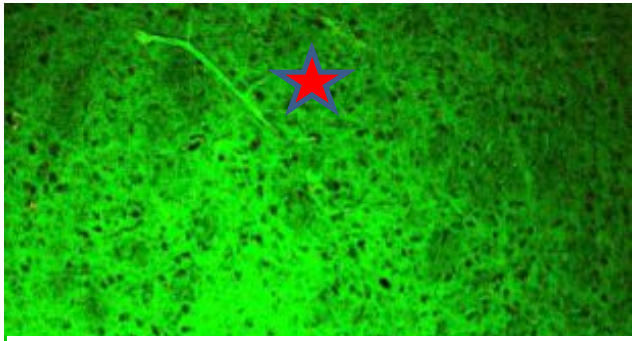
Szentistvanyi I, Patlak CS, Ellis RA, Cserr HF (1984) Drainage of interstitial fluid from different regions of rat brain. American Journal of Physiology 246:F835-844

Perivascular Lymphatic Drainage of Interstitial Fluid and Solutes from the Brain along Basement Membranes (BM) in the Walls of Cerebral Capillaries and Arteries



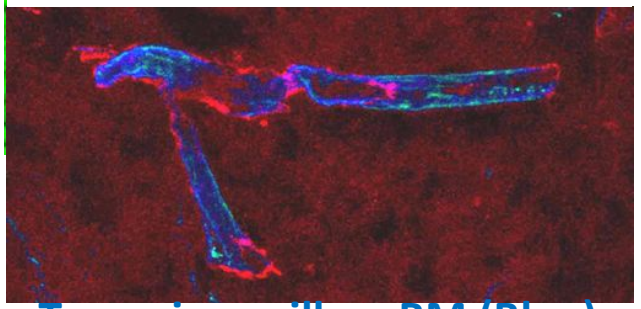
Carare RO, et al (2008) Neuropathol Appl Neurobiol 34:131-144

Hawkes CA, Carare RO, Weller RO. Acta Neuropathol. 2014 Apr;127(4):617-8



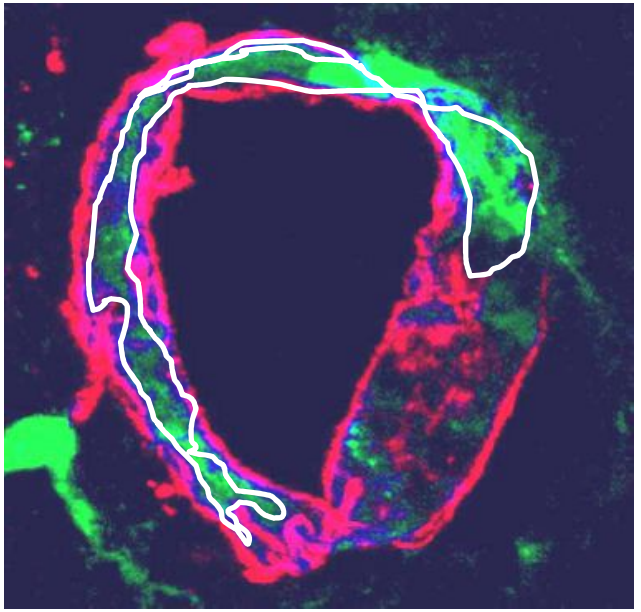
5 mins

Diffuse spread of tracer (Green)



5 mins

Tracer in capillary BM (Blue)



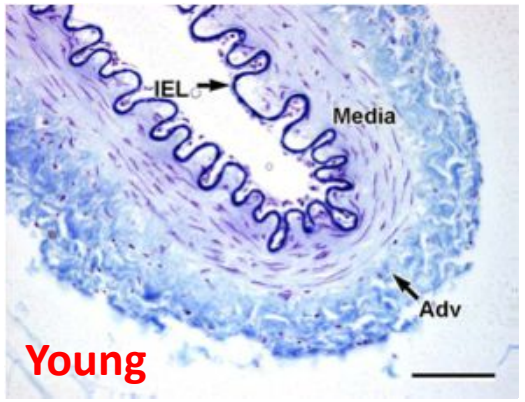
5 mins

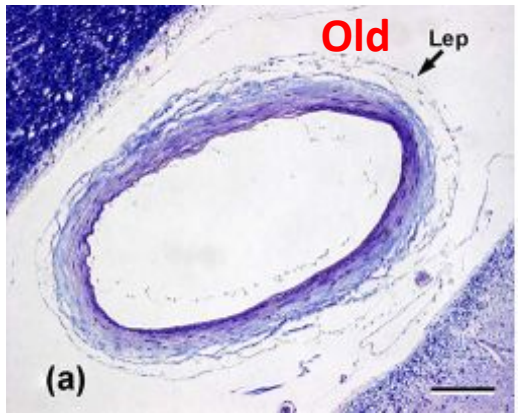
Tracer in BM in artery wall (Blue)

Pathology:

Failure of interstitial fluid drainage with age and Alzheimer's disease

- Motive force for drainage derived from vascular pulsations (*Schley et al 2006; Arbel-Ornath, M et al 2013)*
- Arteries stiffen with age and arteriosclerosis → (Weller et al 2009)





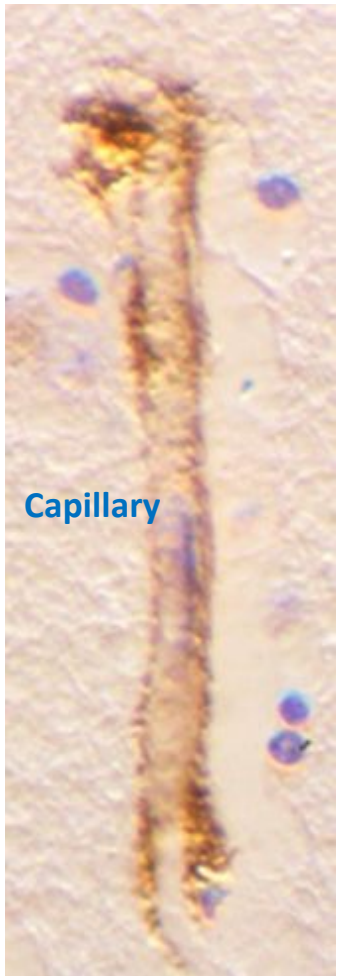
- Pathological Consequences of Age
- Impairment of perivascular drainage *(Hawkes et al 2011)*
- Deposition of amyloid β in perivascular drainage pathways as cerebral amyloid angiopathy *(Weller et al 1998; Carare et al 2013)*
- Deposition of amyloid plaques in the brain parenchyma in Alzheimer's disease
- Loss of homoeostasis with accumulation of fluid and solutes in the brain *Carare et al 2013)*

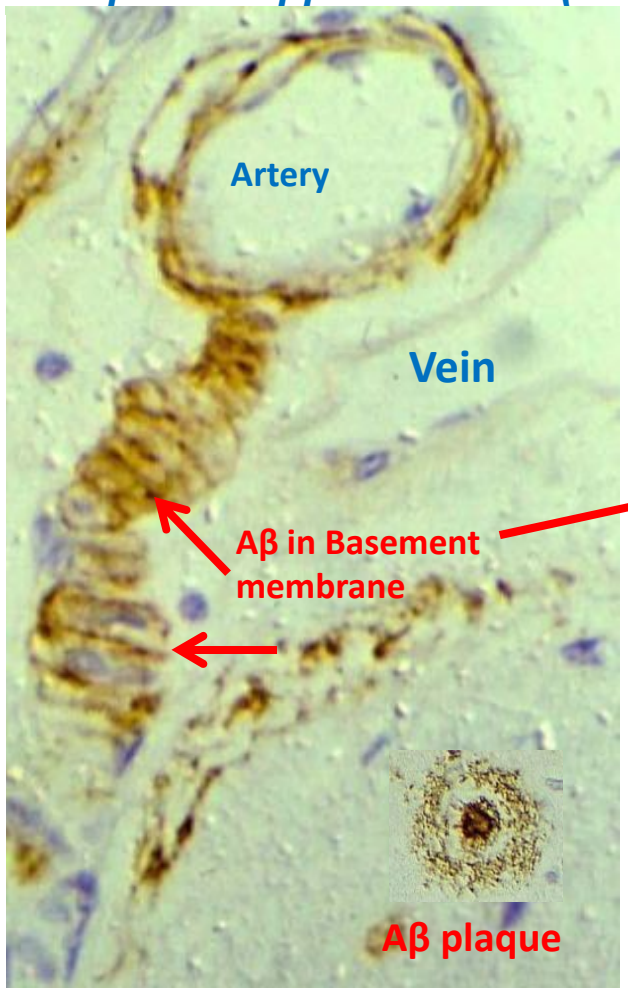
- Increase in severity of CAA in Aβ immunotherapy (Solublised Aβ entrapped in the drainage pathways) *(Boche et al 2008)*

Pathology: Cerebral Amyloid Angiopathy (CAA) in Humans

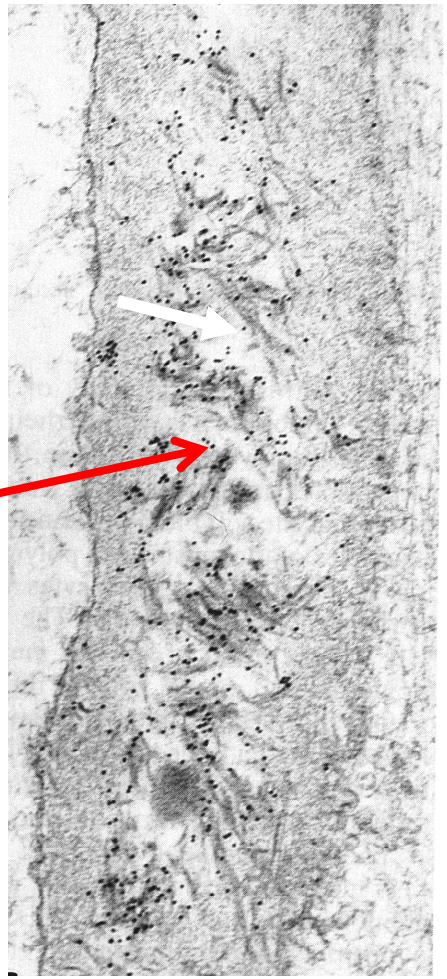
Amyloid-β accumulates in perivascular lymphatic drainage pathways in Basement Membranes in the walls of Capillaries and Arteries

(Preston SD et al Neuropathol Appl Neurobiol (2003) 29: 106-117)





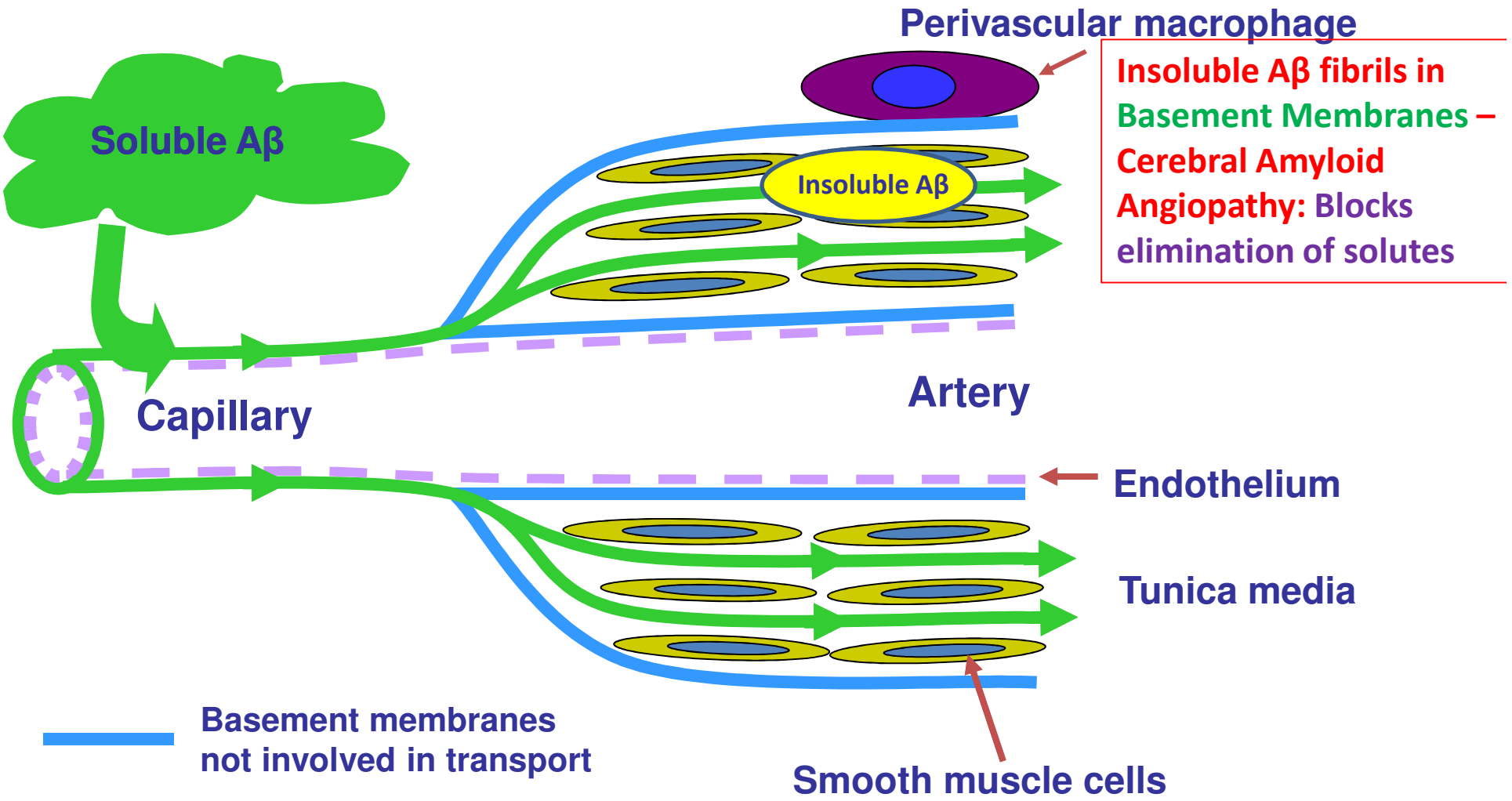
(Aβ is Brown)



TEM Aβ in Basement Membrane – (Wisniewski HM 1995)

CAA defines drainage pathways in Human Brain

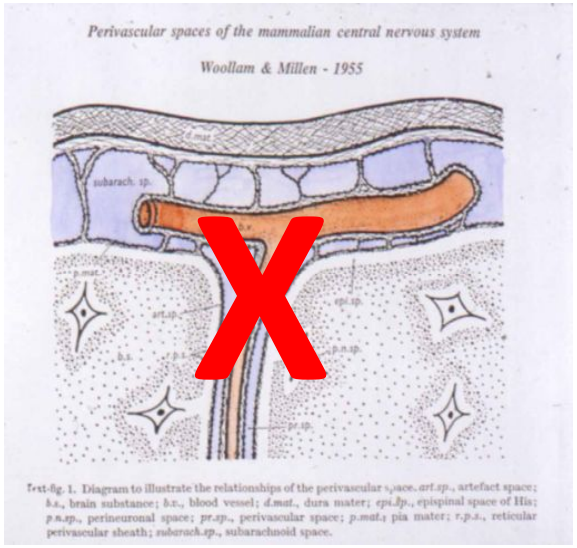
Perivascular (lymphatic) drainage of interstitial fluid and solutes along basement membranes of capillaries and arteries and its failure in Cerebral Amyloid Angiopathy and Alzheimer's disease

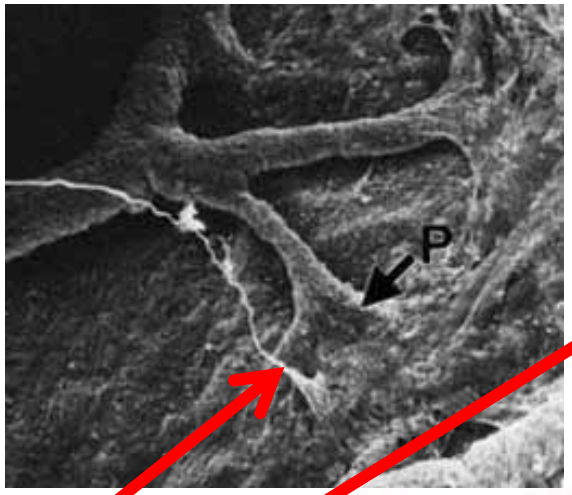


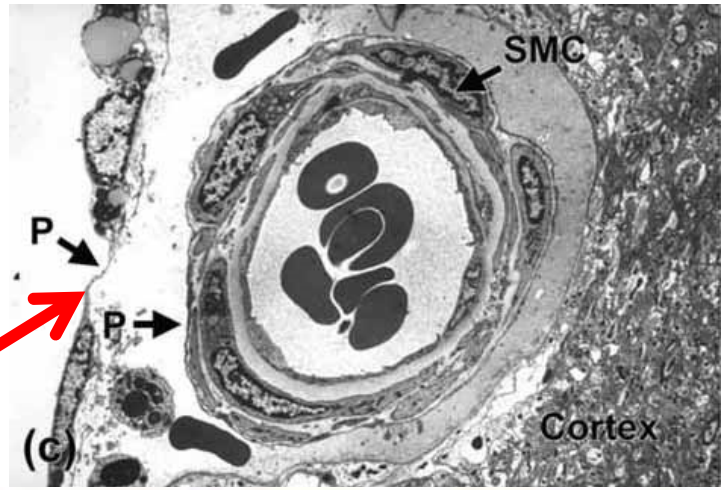
Weller RO et al (2008) Brain Pathology 18:253-266 *Hawkes CA, et al (2011). Acta Neuropathologica 2011;121:431-43*.

Connections between CSF and the brain in Humans

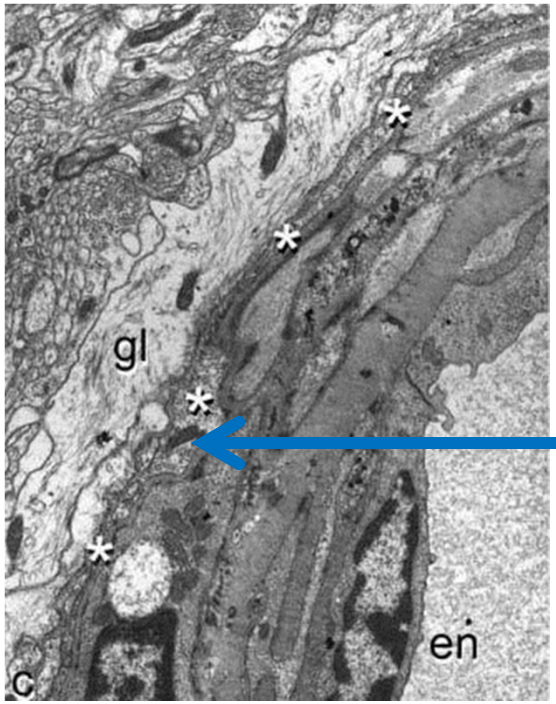
Pia mater on the surface of Human Cerebral Cortex and lack of Vichow-Robin space





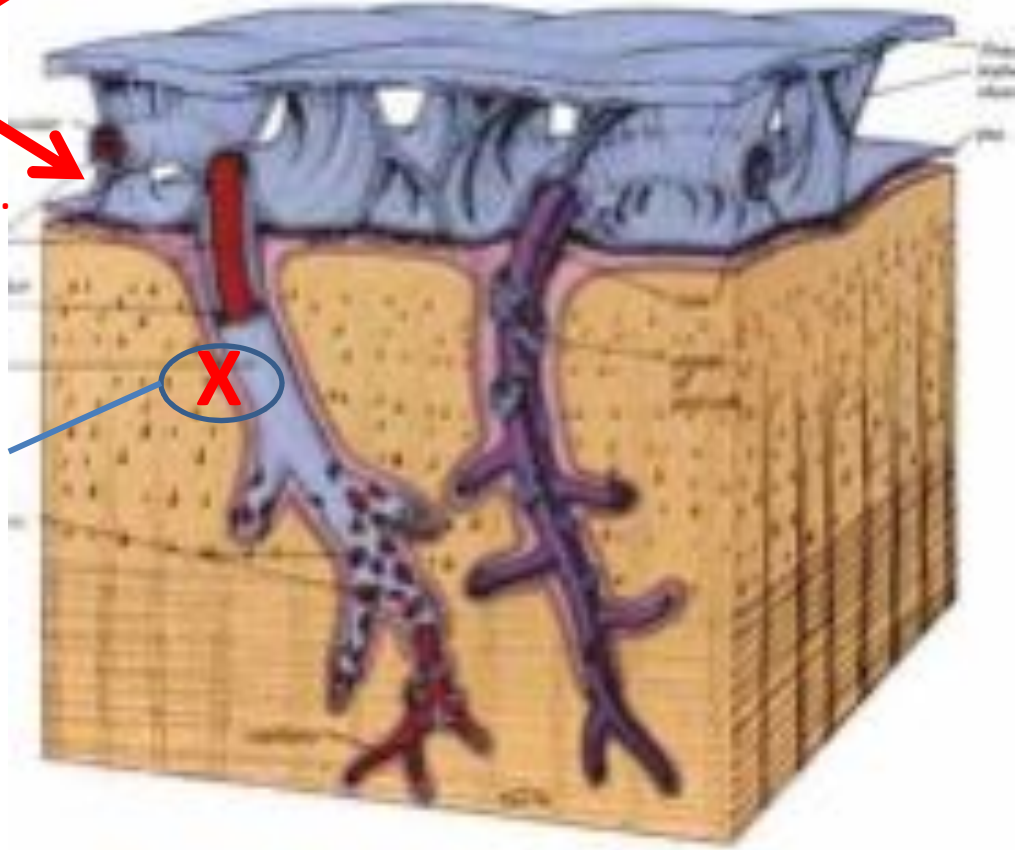


Pia mater separates subarachnoid space from brain.



Artery in Human Cortex

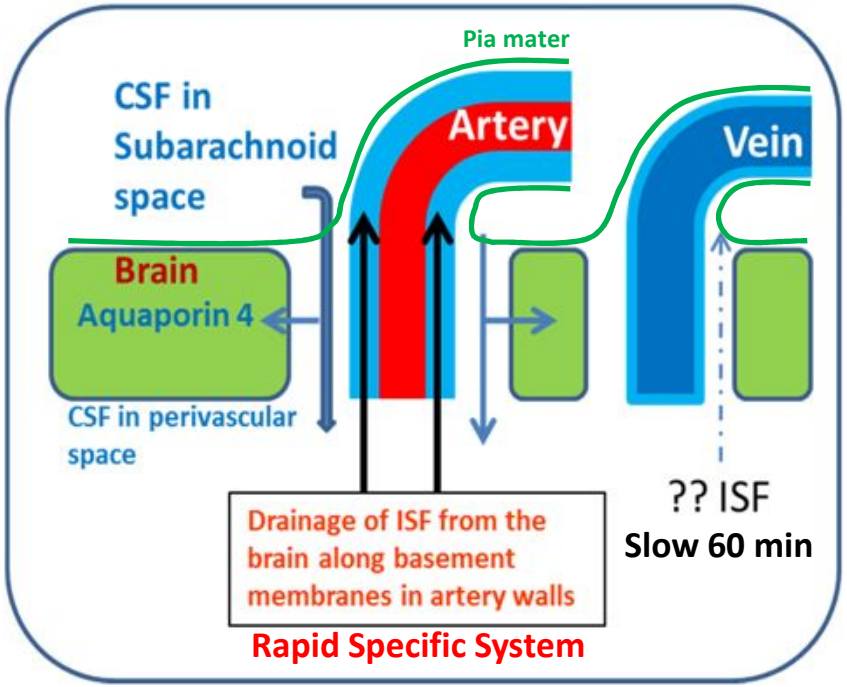
No perivascular (Virchow-Robin) space in Human cortex
But perivascular spaces in Basal Ganglia and White matter



Connections between CSF and Interstitial Fluid (ISF)

Convective tracer influx: (Rennels , et al 1985)
Glymphatics (Iliff, Nedergaard et al 2012-2014)

- Para-arterial entry into brain of tracers in CSF
- Extension of tracer along vascular tree.
- Entry of solutes into the brain parenchyma regulated by:
  - Arterial pulsations
  - molecular weight of tracer
  - glial Aquaporin 4.

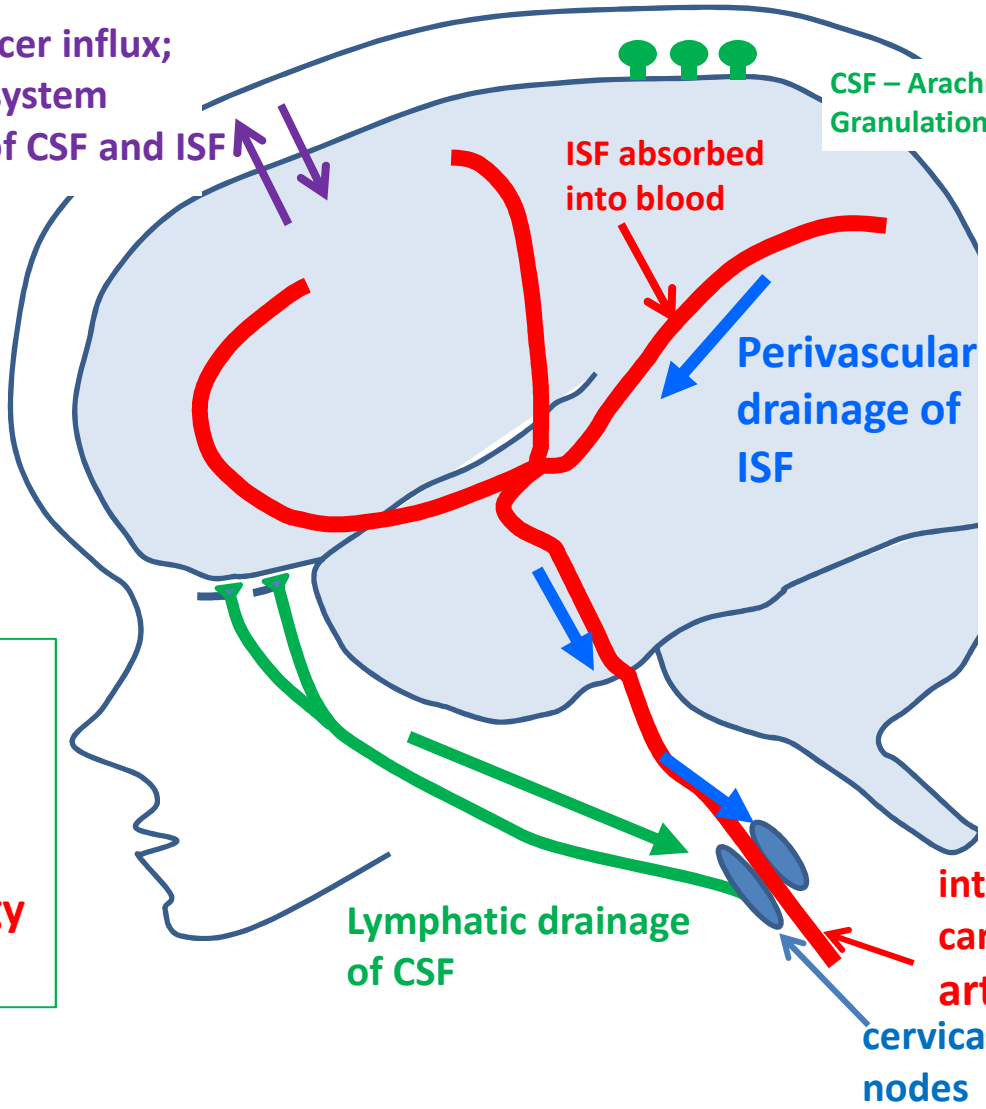


SLOW Non-specific equilibration of tracers from CSF with ISF
in 30 min. Elimination 1-2 hours

Compare:

RAPID SPECIFIC System of perivascular lymphatic drainage along basement membranes in capillary and artery walls (< 5mins)

Drainage of CSF and Interstitial Fluid (ISF) from the Brain



SLOW non-specific equilibration of CSF and ISF
No Pathology identified as yet

Lymphatic drainage of CSF: Allows traffic of APCs to lymph nodes. **Pathology** Hydrocephalus

Perivascular drainage of ISF and solutes
RAPID Specific response system for clearance along Vascular Basement Membranes
Pathology:
Failure with Age:
CAA and Alzheimer's disease

Acknowledgements

I thank the many students and colleagues who have collaborated in studies of the meninges, CSF and Interstitial Fluid drainage and in particular,

Roxana Carare, and Cheryl Hawkes

Funding: MRC; MS Society; Alzheimer's Research UK