New view on the CSF circulation: CSF production and CSF absorption by brain capillaries

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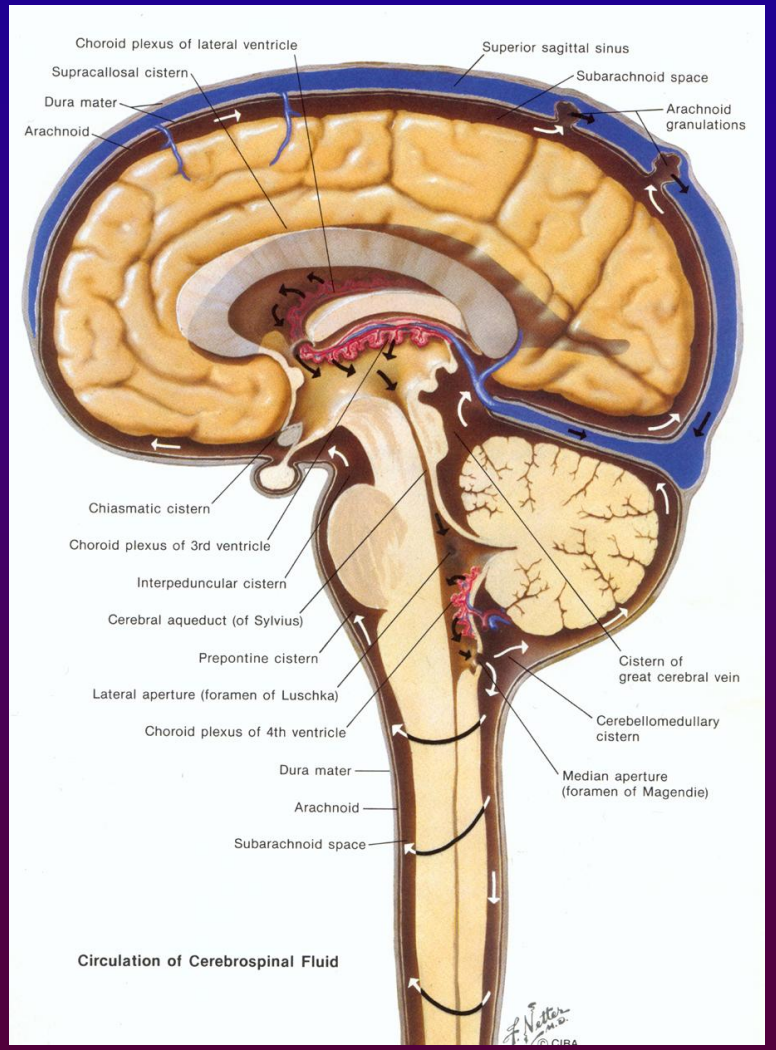
Stockholm, Sweden

Major differences between the new and old concept of CSF circulation

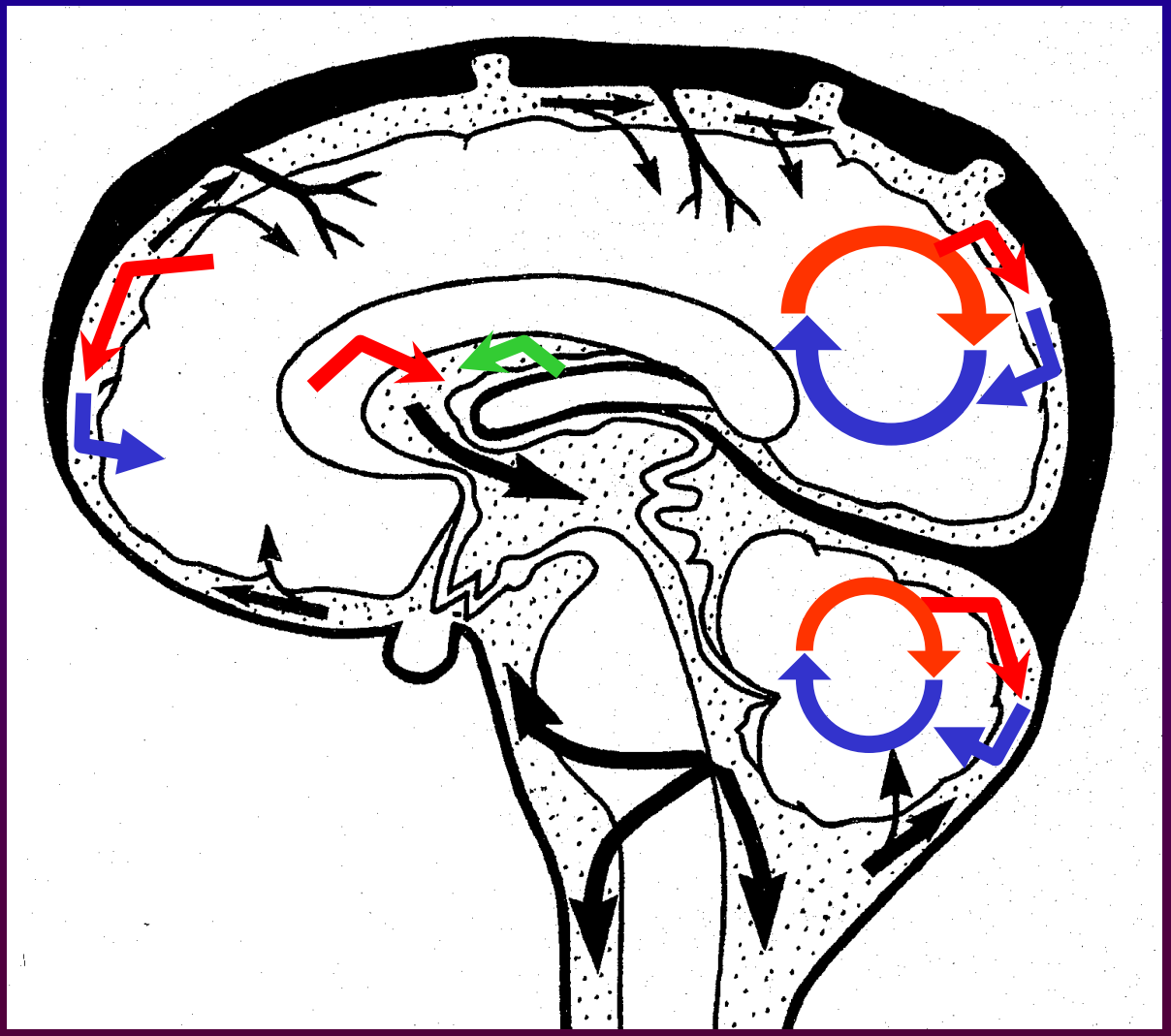
Normal CSF circulation
old CSF bulk flow model

- There is bulk flow of CSF from the intraventricular plexus to the arachnoid granulations



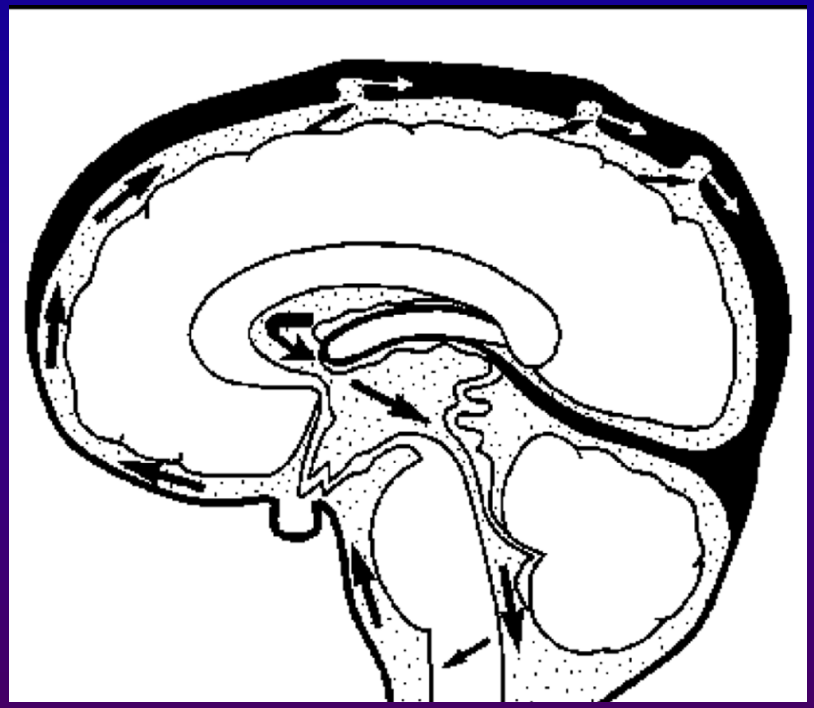
Normal CSF circulation
New model

The CSF is produced and absorbed by the brain capillaries



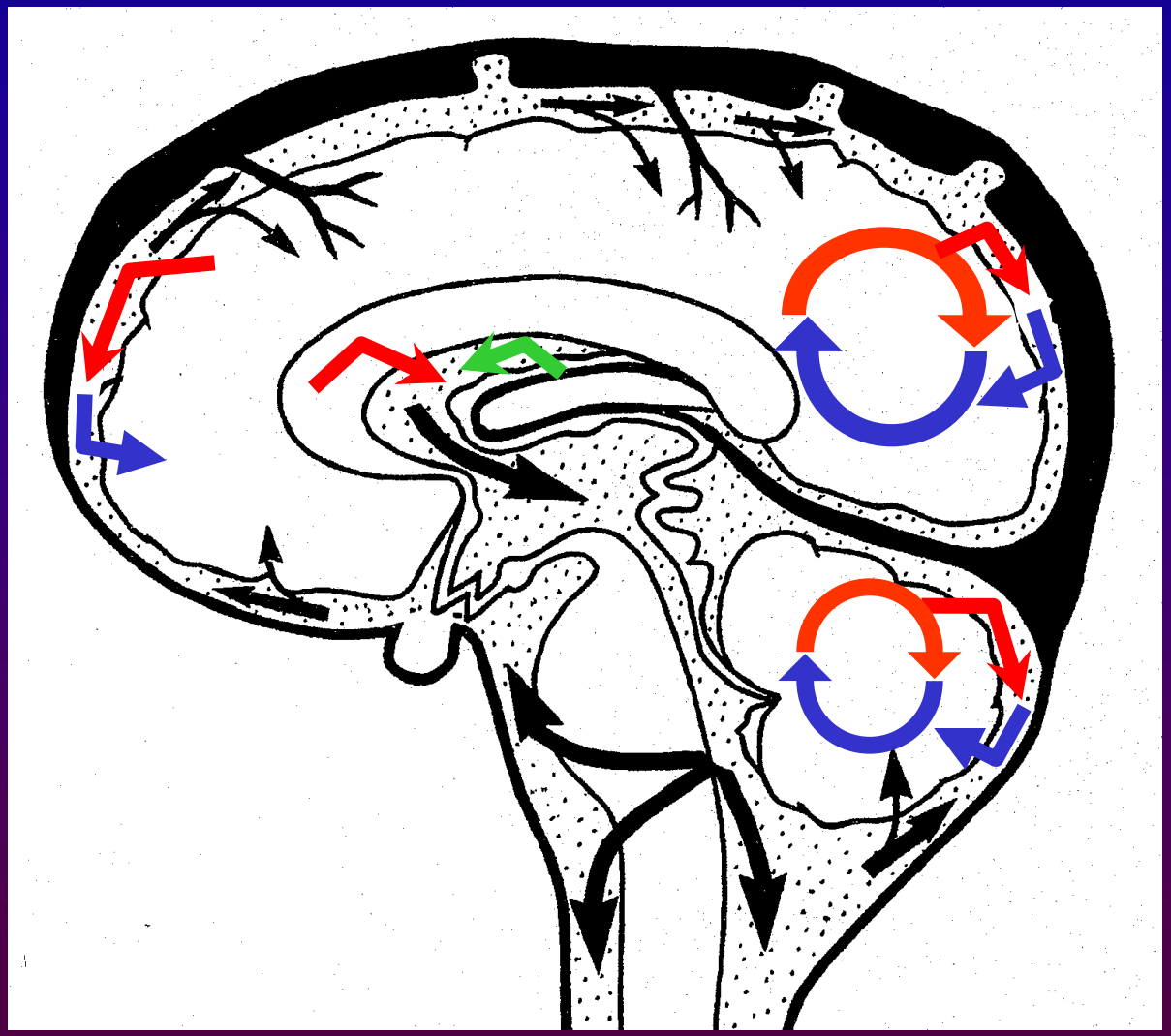
CSF production and CSF absorption

Bulk flow model



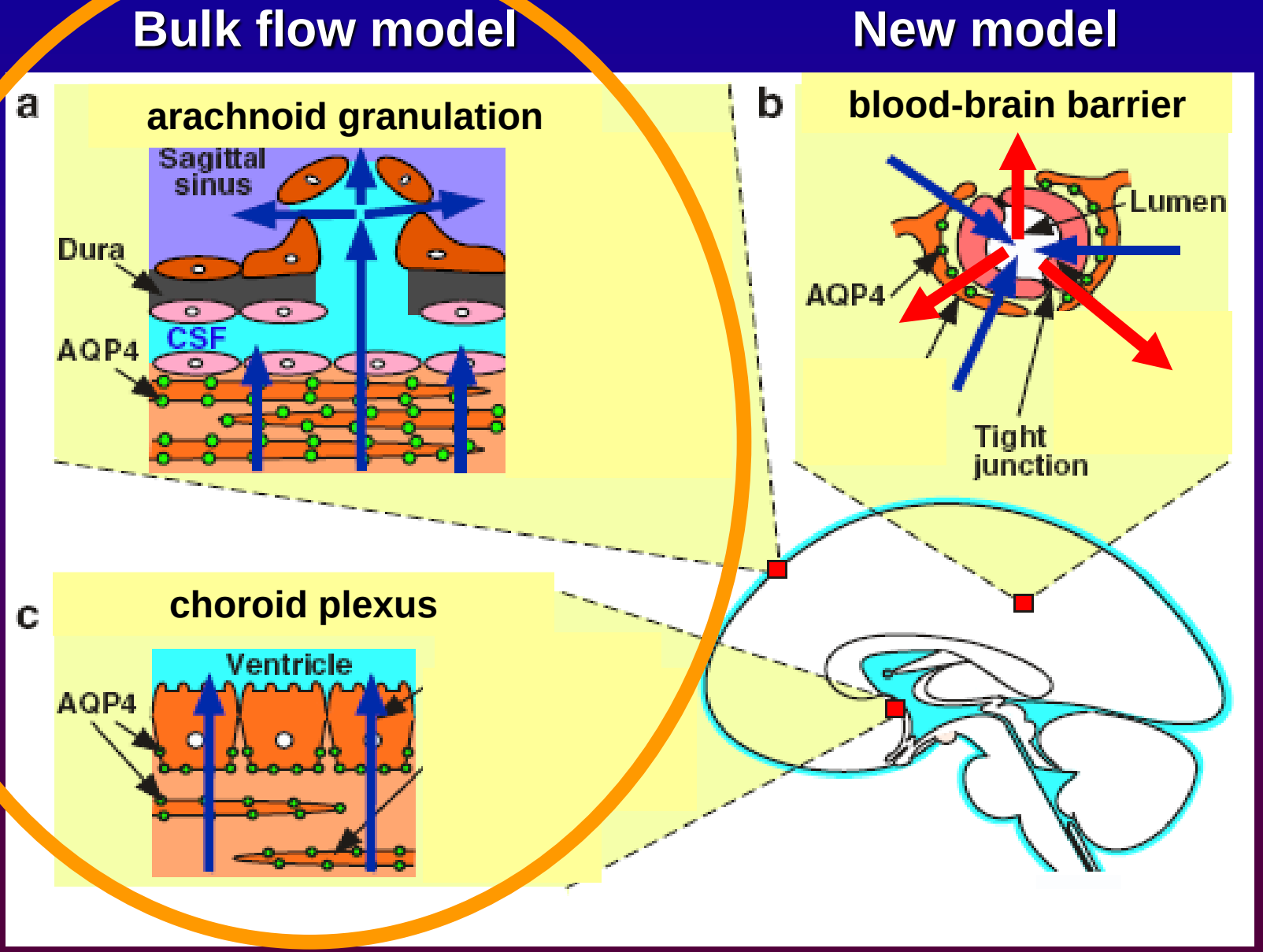
The CSF is produced by
the choroid plexus
and absorbed by
the arachnoid granulations

New model

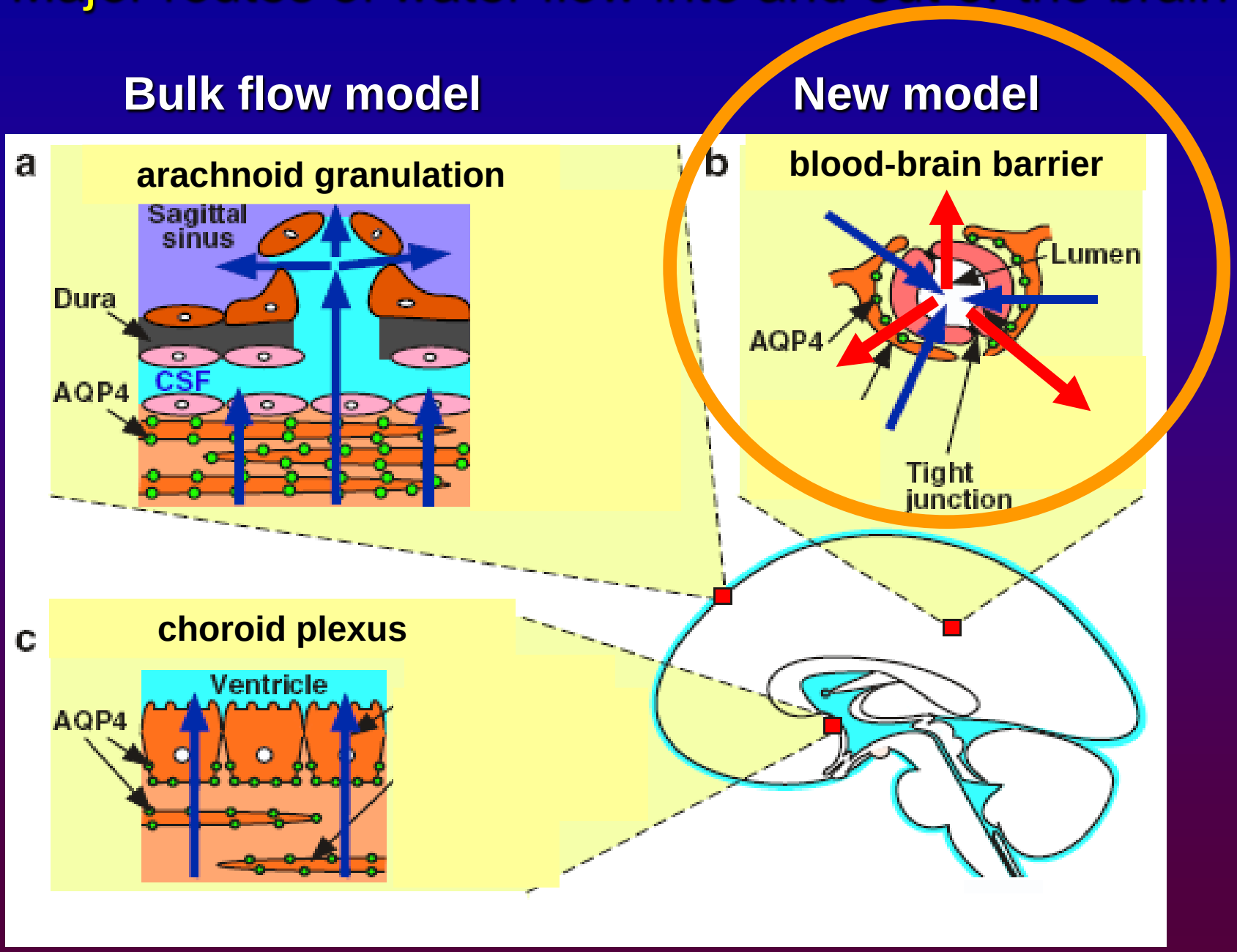


The CSF is produced and absorbed by the brain capillaries

Major routes of water flow into and out of the brain



Major routes of water flow into and out of the brain



New Concept of CSF Circulation

1. The CSF is absorbed by the brain capillaries

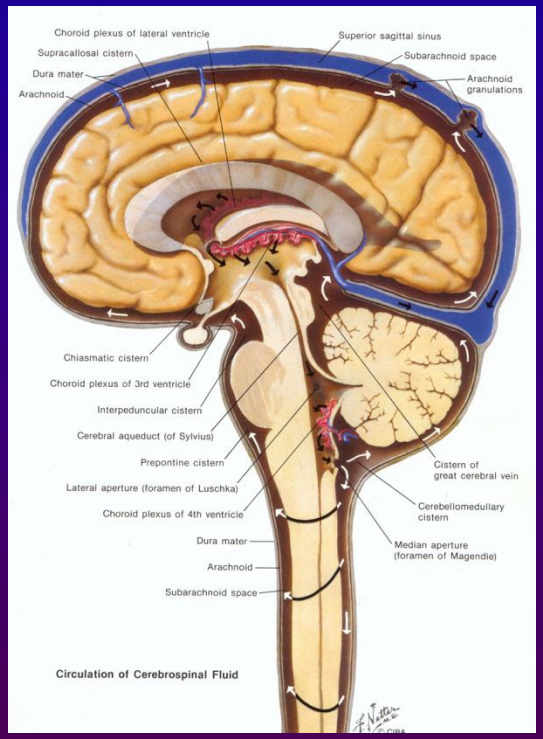
2. The major part of the CSF is produced by the brain capillaries

New Concept of CSF Circulation

1. CSF absorption by brain capillaries
2. CSF production by brain capillaries

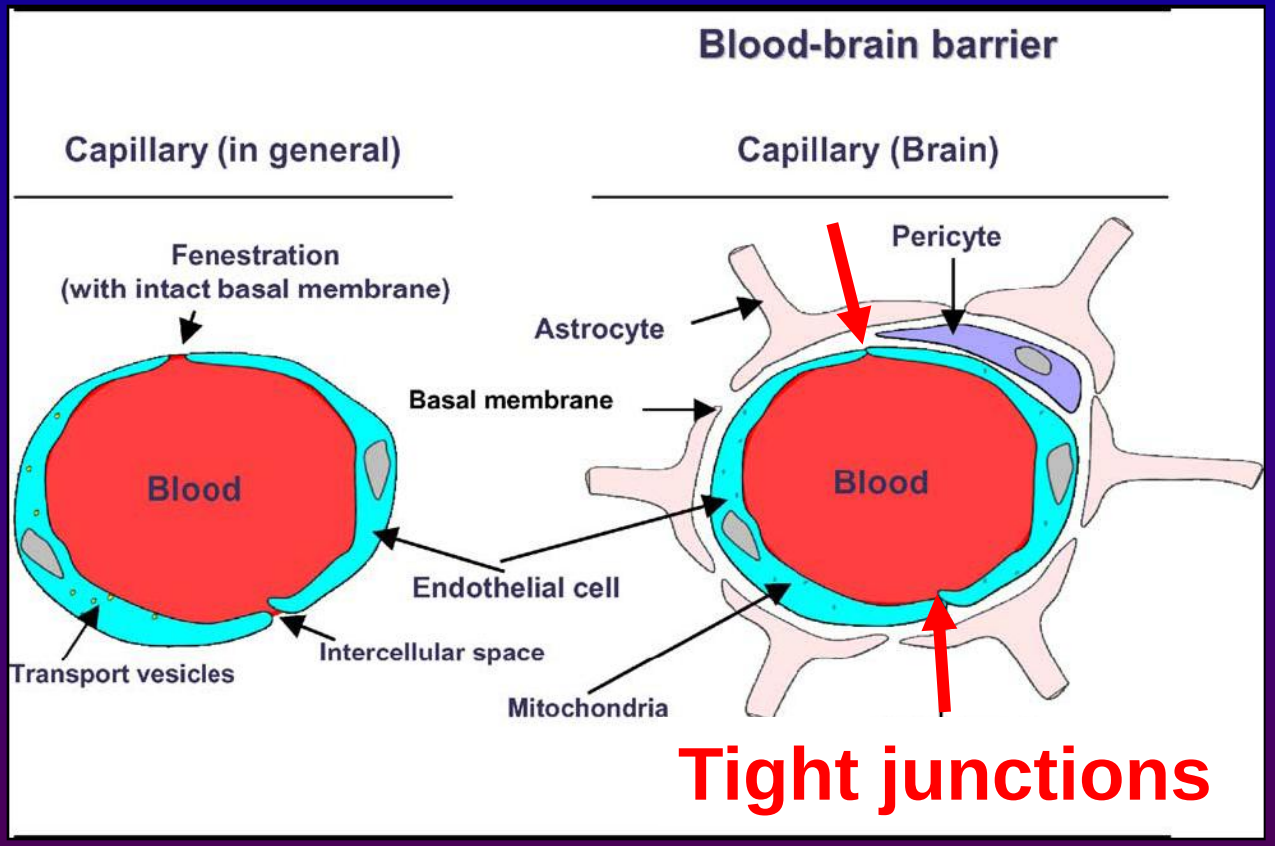
The CSF bulk flow model

is based on the assumption that the arachnoid granulations absorb all proteins and macromolecules in the CNS and that –



brain capillaries are impermeable to macromolecules !

Blood-brain barrier



Due to the tight junctions, the BBB is almost impermeable to water-soluble molecules

Can they pass in the other direction from brain-to-blood?

Albumin transport from CSF to blood

Rapid elimination of albumin from the CSF

Rapid transport of albumin from CSF to plasma – half-time max in plasma occurs at 90 min

Rapid transport of albumin from the CSF into the brain

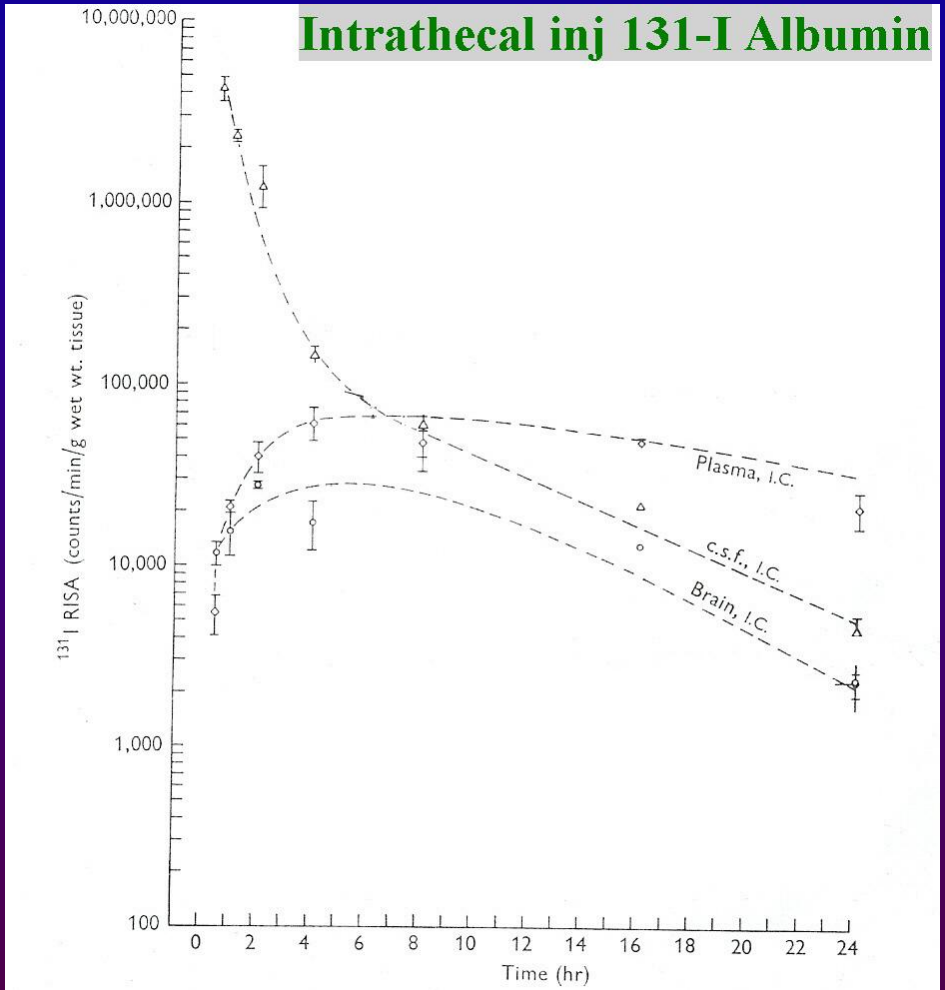


Fig. 7. Radioactivity of brain, muscle, c.s.f., and plasma water from 30 min to 24 hr after injection of RISA.

Reed & Woodbury: J Physiol 1963

Inulin transport from CSF to blood

Rapid elimination of inulin from the CSF

Rapid transport of inulin from CSF to plasma – half-time max in plasma 60 min

Rapid transport of inulin from the CSF into the brain

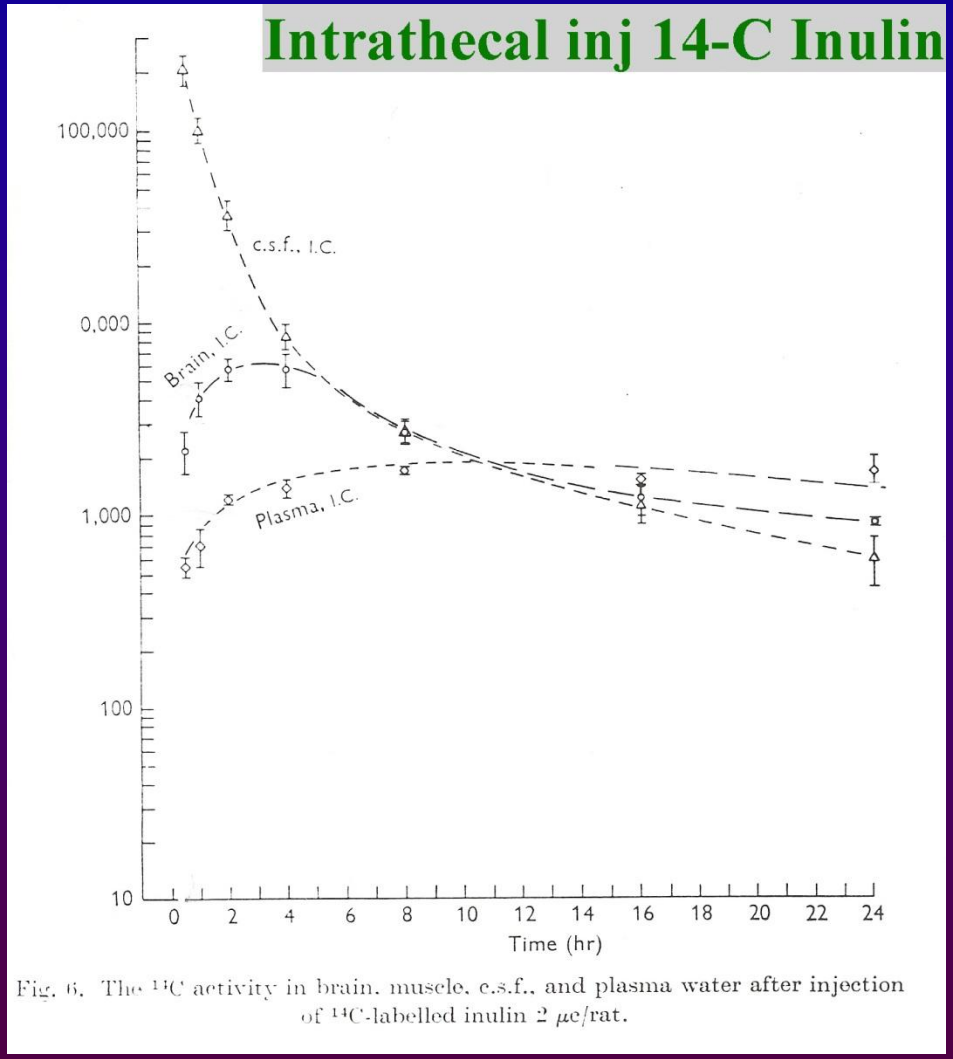


Fig. 6. The ^{14}C activity in brain, muscle, c.s.f., and plasma water after injection of ^{14}C-labelled inulin 2 μc/rat.

Reed & Woodbury: J Physiol 1963

Albumin transport from blood to CSF

After i.v. injection, there is a small but significant transport of albumin from the blood to the CSF and to the brain

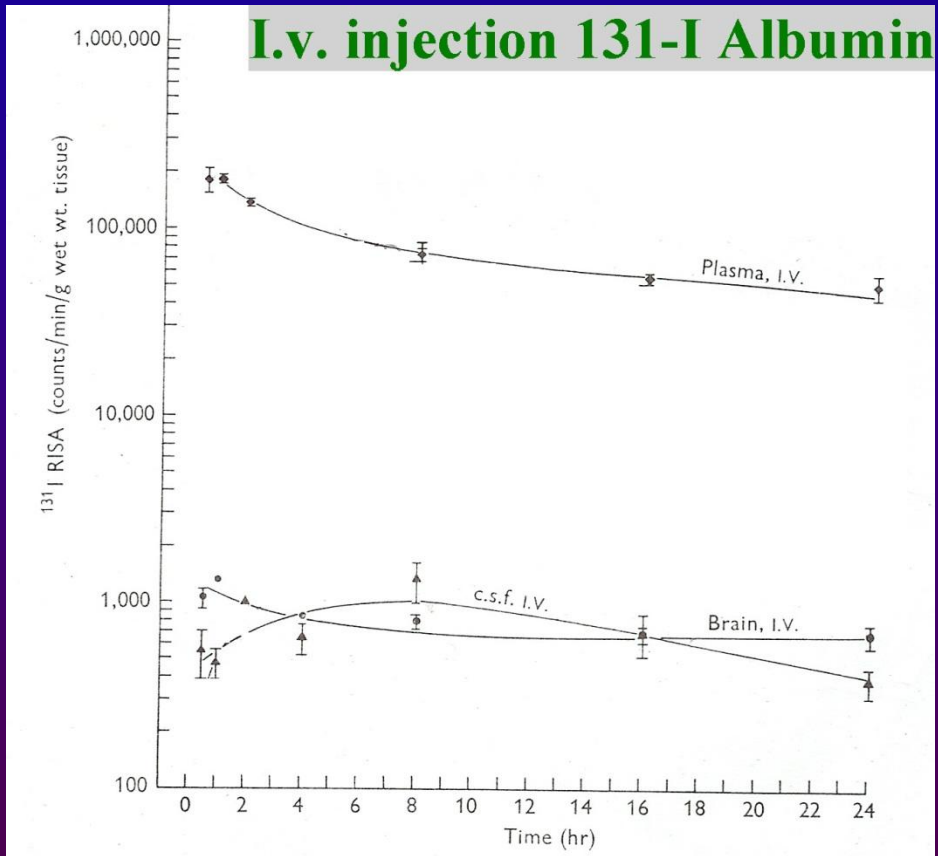


Fig. 7. Radioactivity of brain, muscle, c.s.f., and plasma water from 30 min to 24 hr after injection of RISA.

Reed & Woodbury: J Physiol 1963

Absorption of contrast medium from CSF to blood

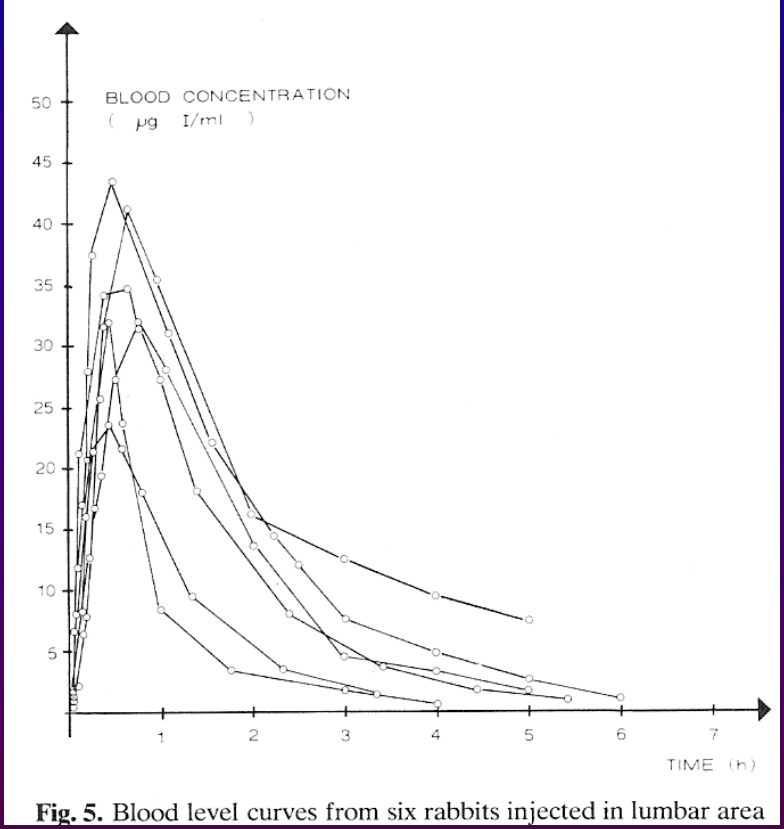


Fig. 5. Blood level curves from six rabbits injected in lumbar area

Blood concentration curve

At myelography in rabbits, there is a rapid transport of contrast from CSF to blood

Peak concentration in blood occurs within 1 hour

Golman K: Neuroradiology 1979

Absorption of contrast medium from CSF to blood

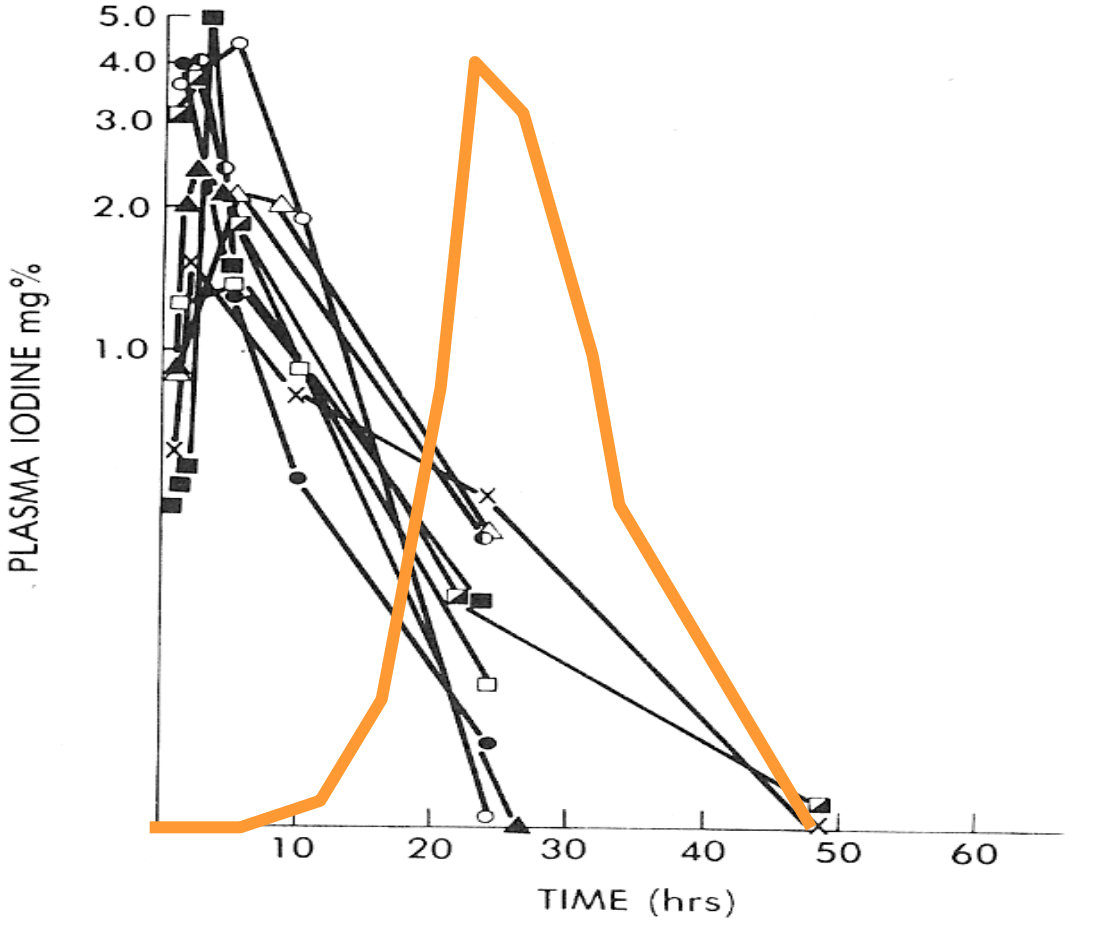


Fig. 2. Semilog plot of serial plasma iodine levels in 9 control patients.

Blood concentration curve

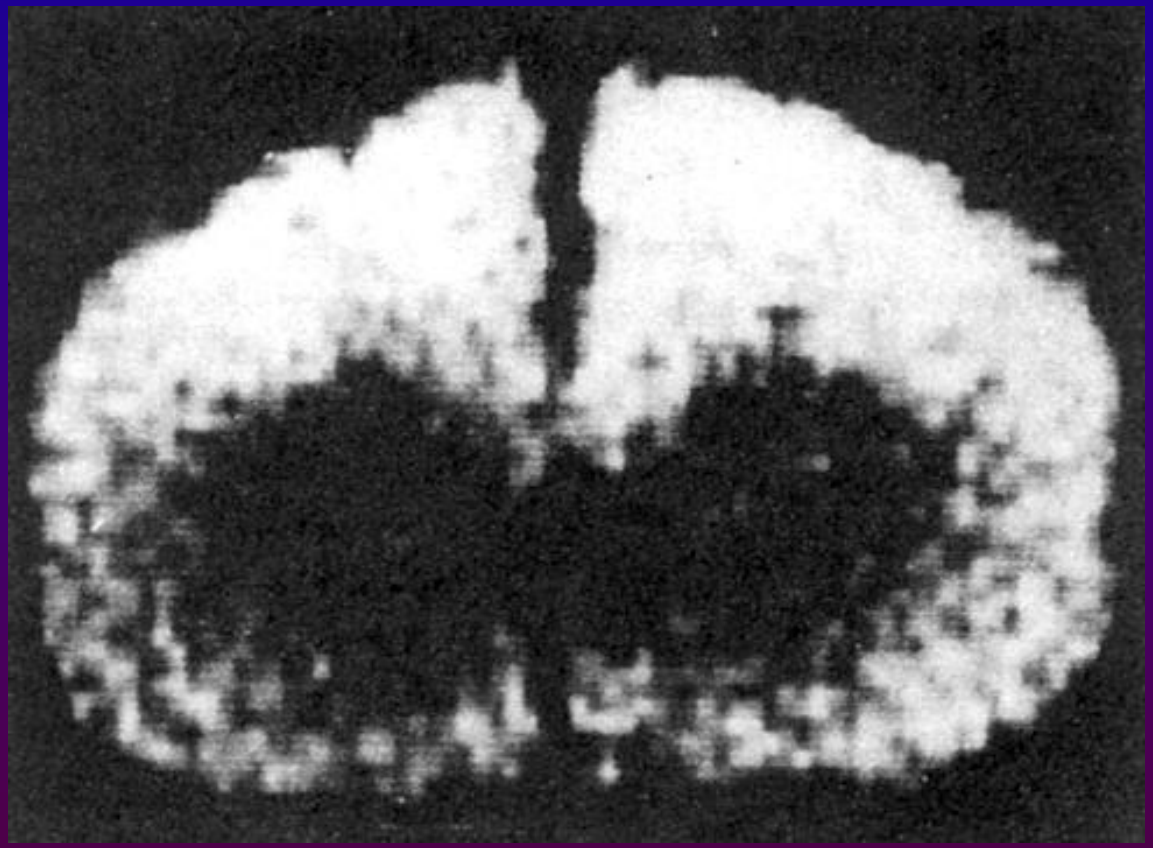
At myelography in humans, there is a rapid transport of contrast from CSF to blood

Peak concentration in blood occurs within 2 hours

CT-cisternography (yellow): convexity-maximum occurs at 24h

Enzmann D: Radiology 1979

Rapid transport of contrast medium into the brain cortex

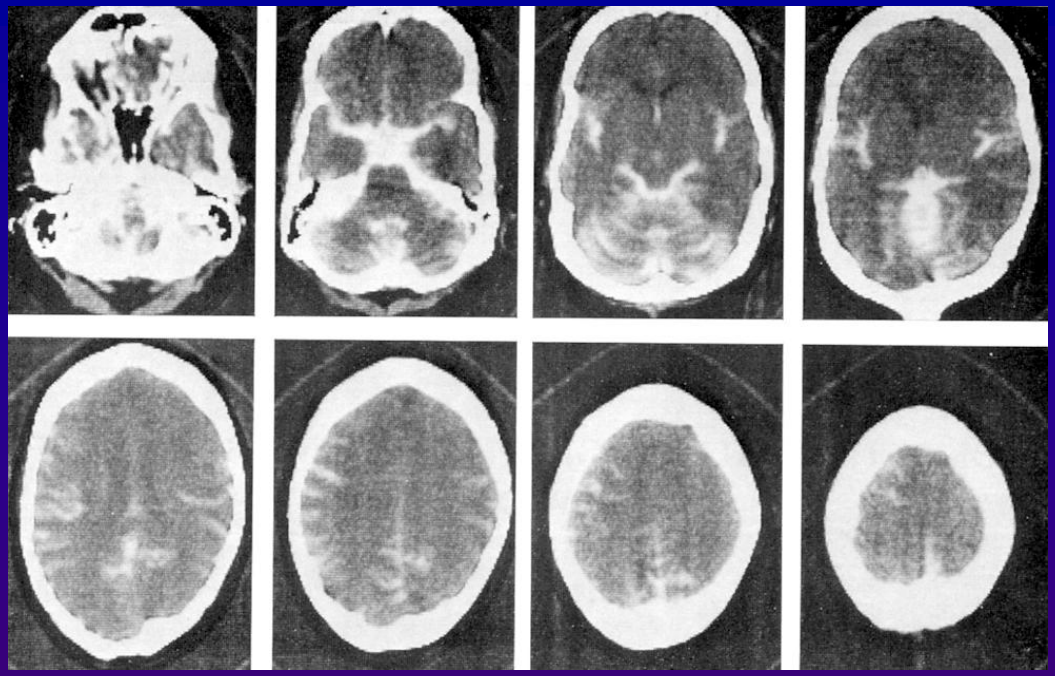


1 hour after i.c. injection in rabbit

Sage M: AJR 1983

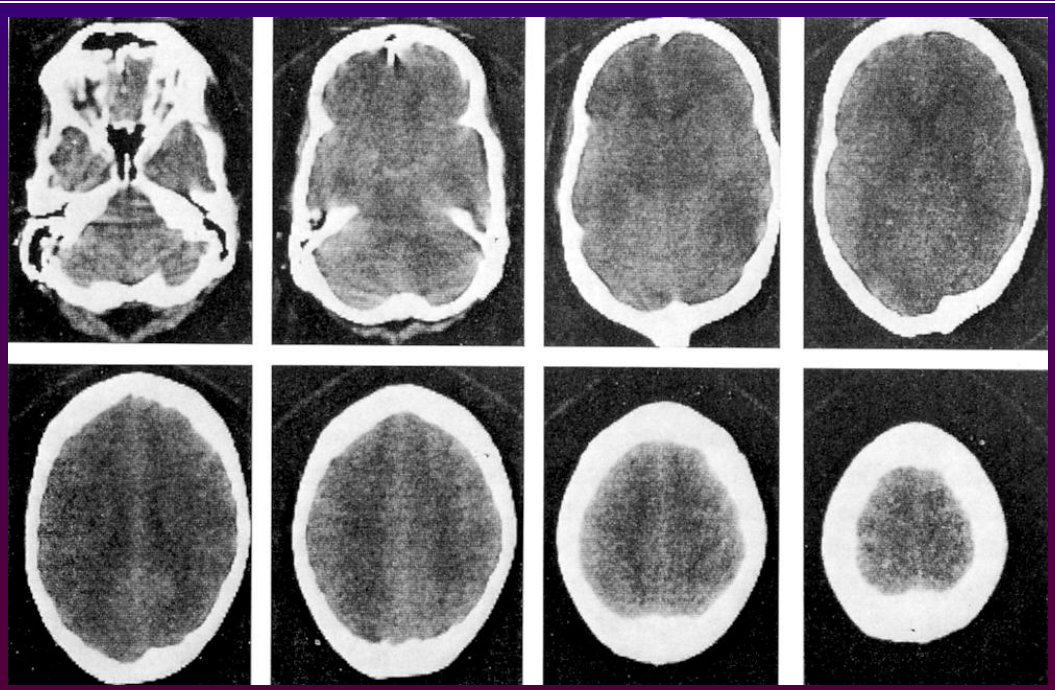
CT-cisternography

3 hours



At 3 hours,
there is penetration of
the contrast medium
into the brain cortex

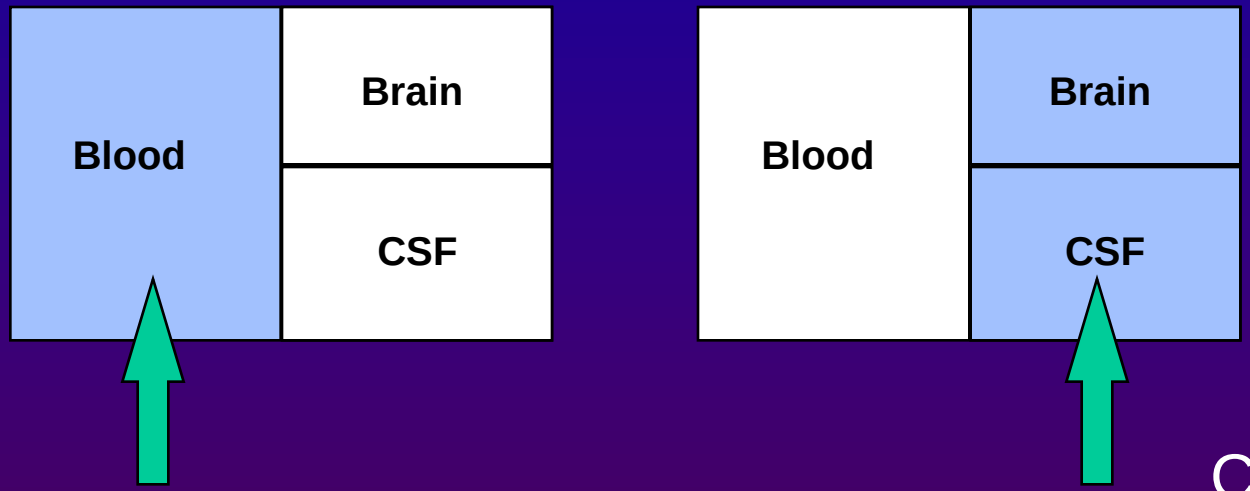
24 hours



At 24 hours,
almost all contrast is
located in brain tissue

T. Hindmarsh

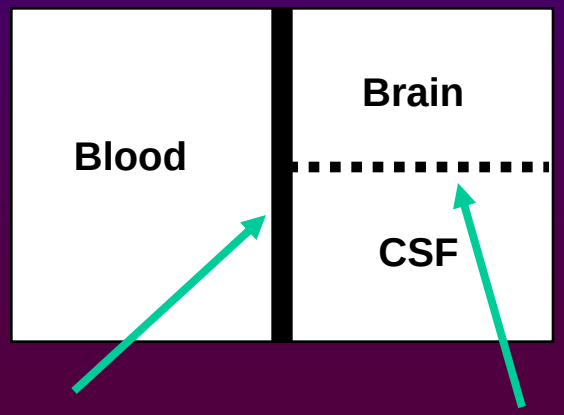
Blood brain barrier?



Non diffusible colour tracer

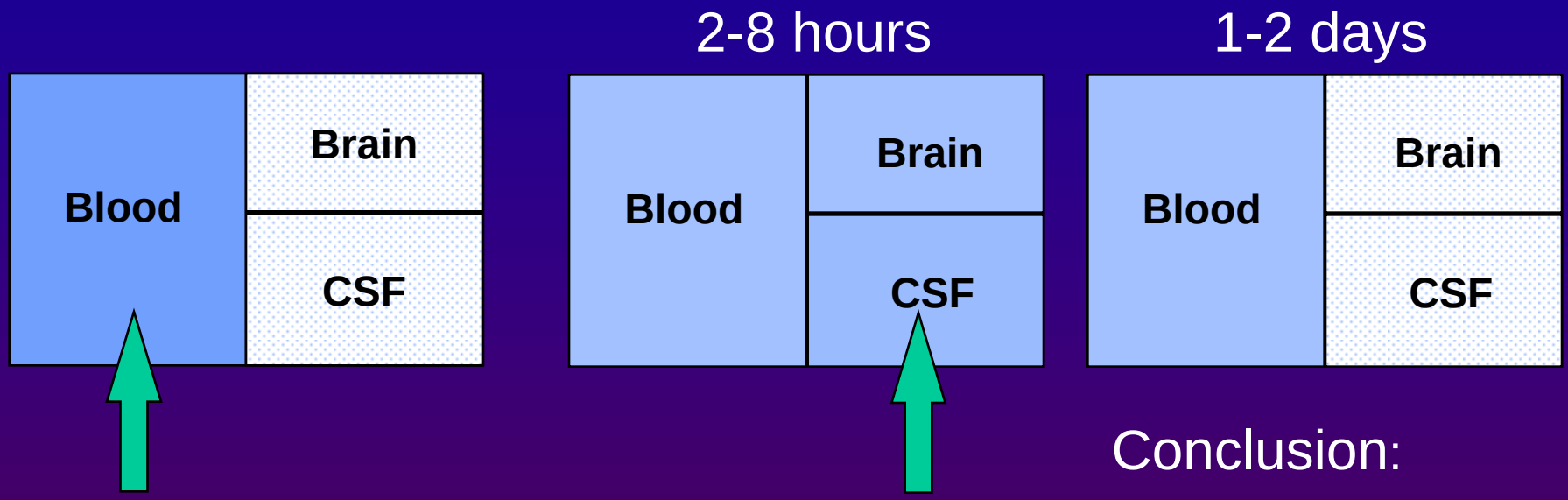
Ehrlich 1885 and Goldmann 1913

Conclusion:



Impermeable to dye Permeable to dye

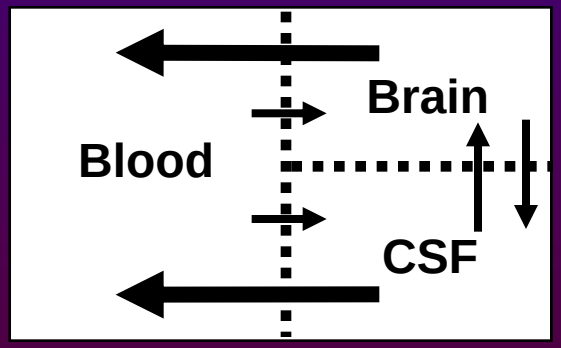
Blood brain barrier



Inulin, albumin, Iodine, contrast media

Reed & Woodbury 1963

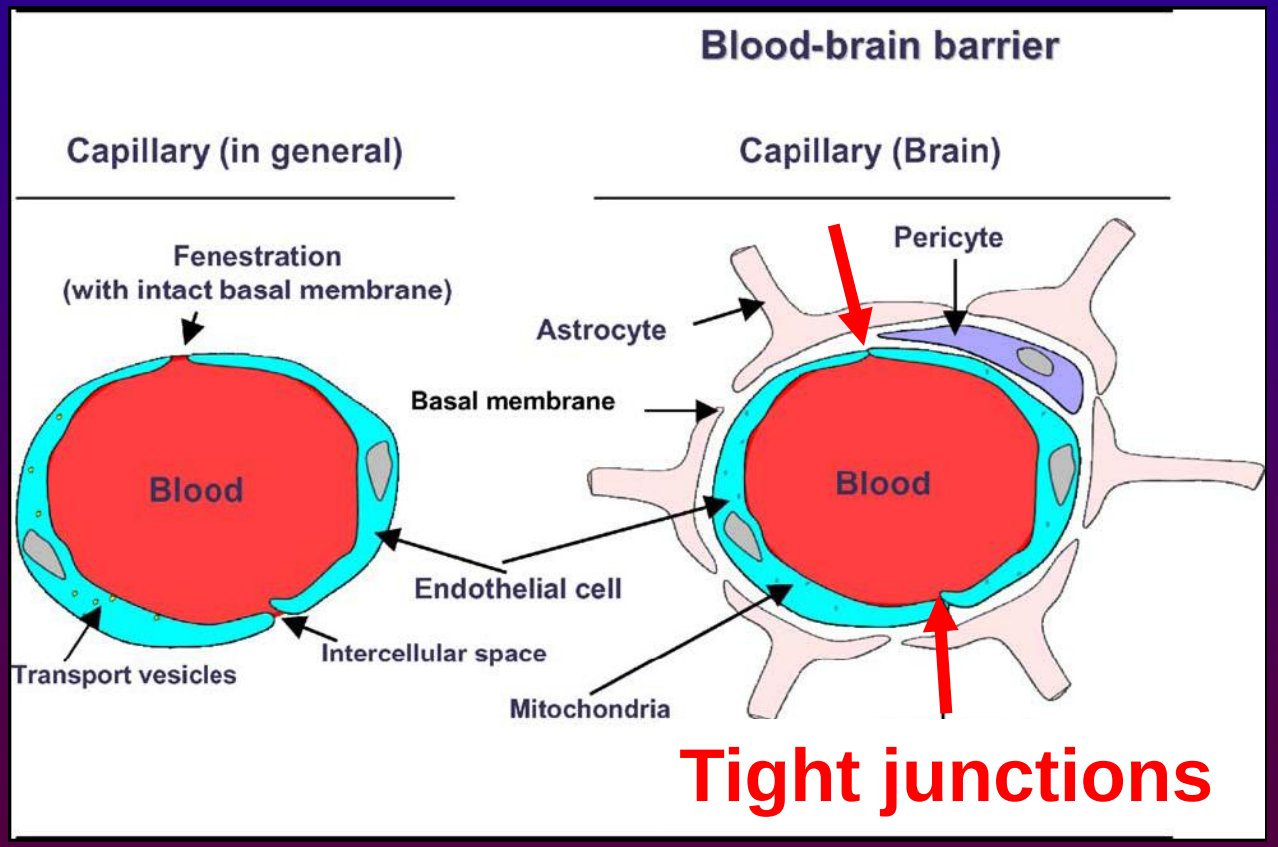
Conclusion:



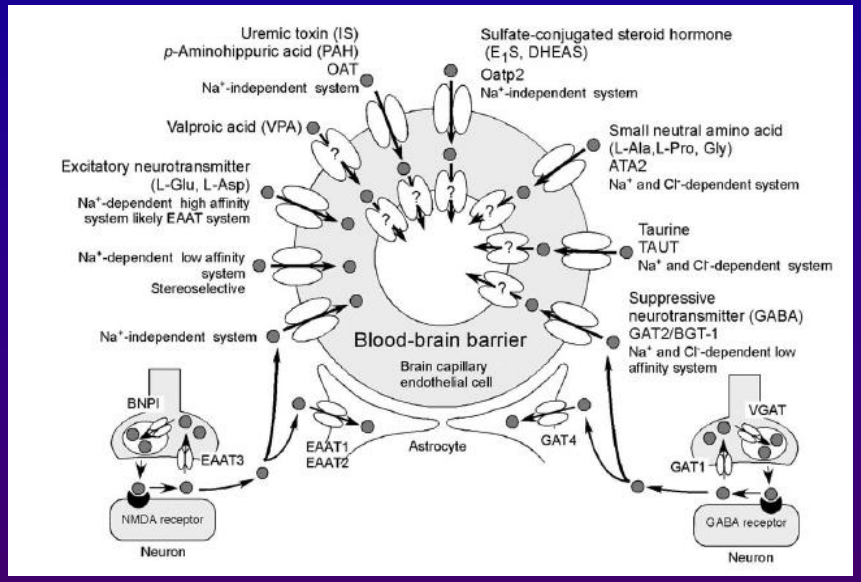
Rapid transport from CNS to blood

D Greitz 1993

What is the biological substrate for the active transport at the BBB ?

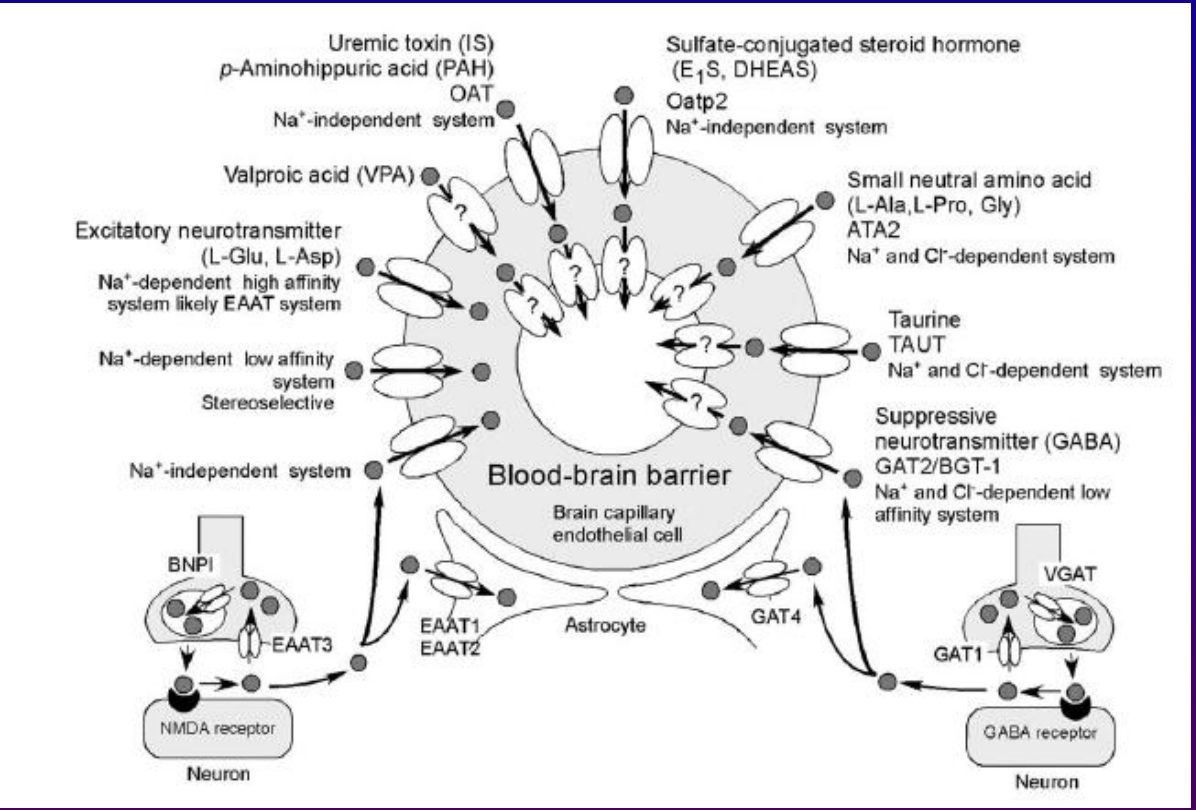


Several brain to blood efflux transporters have been discovered at the BBB



- Betz discovered the first efflux transporter of amino acids (1978)
  - since then 40 different efflux transporters have been identified

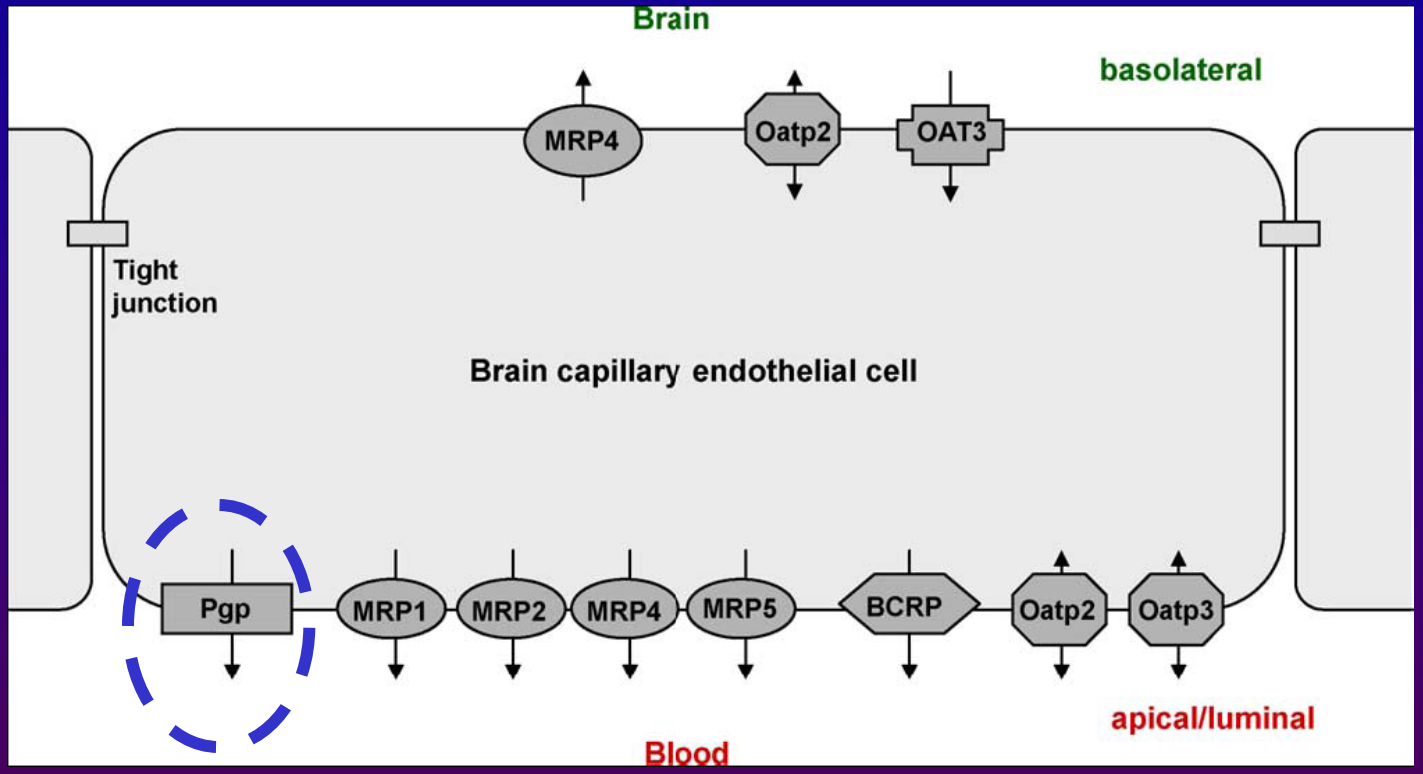
Brain to blood efflux transporters



transport numerous of endogenous and exogenous molecules

from the brain to the blood

Brain-to-blood efflux transporters



Immuno-fluorescence study of P-glycoprotein

Löscher 2005

ELSEVIER

International Journal of Pharmaceutics 248 (2002) 15–29

international journal of pharmaceutics

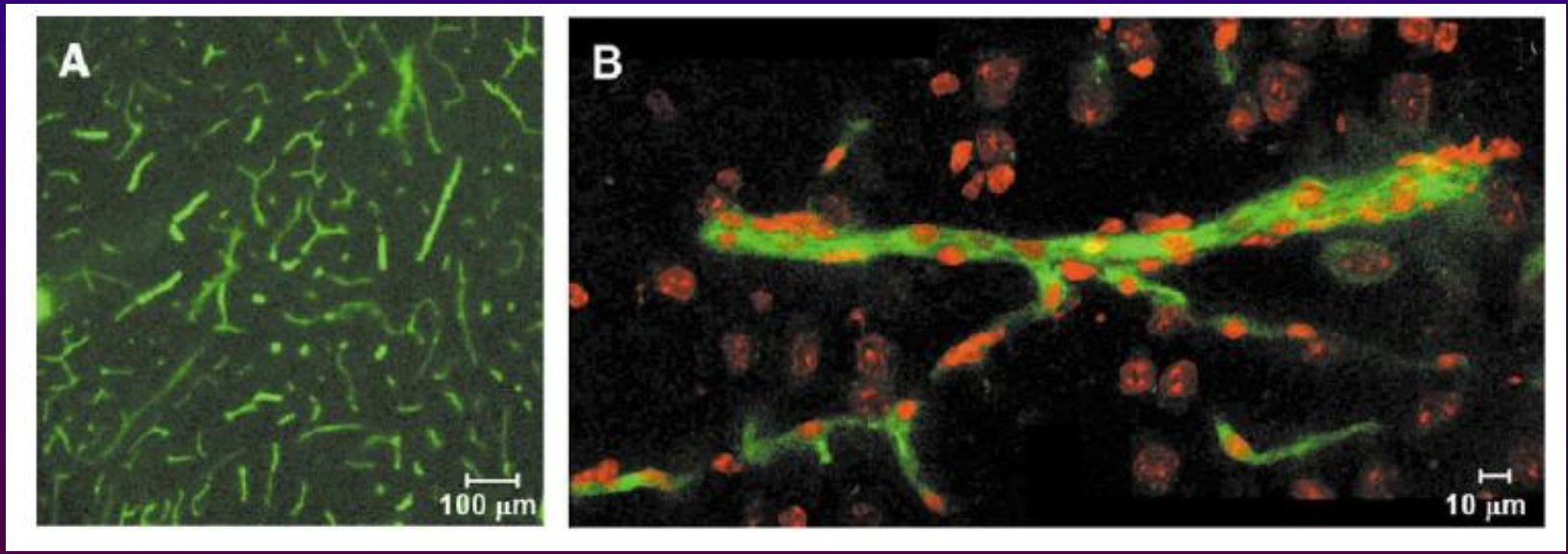
www.elsevier.com/locate/ijpharm

Review

Recent advances in the brain-to-blood efflux transport across the blood–brain barrier

Ken-ichi Hosoya [a,b], Sumio Ohtsuki [b,c,d], Tetsuya Terasaki [b,c,d,*]

Capillary wall



Multidrug transporter P-glycoprotein (fluorescence green)

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Advanced Drug Delivery Reviews 36 (1999) 195–209

advanced drug delivery reviews

The blood–brain barrier efflux transporters as a detoxifying system for the brain

Tetsuya Terasaki*, Ken-ichi Hosoya

Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Tohoku University, Aramakiaza, Aoba, Sendai 980-8578, Japan

The efflux transporters act as a detoxifying system for the brain

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Advanced Drug Delivery Reviews 36 (1999) 195–209

advanced drug delivery reviews

The blood–brain barrier efflux transporters as a detoxifying system for the brain

Tetsuya Terasaki*, Ken-ichi Hosoya

Half-time disappearance rate from brain:

12 min for PAH

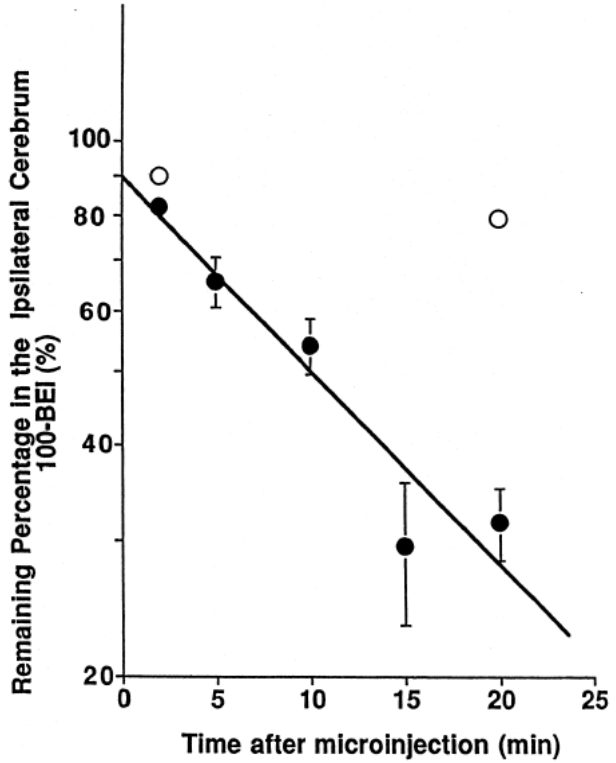
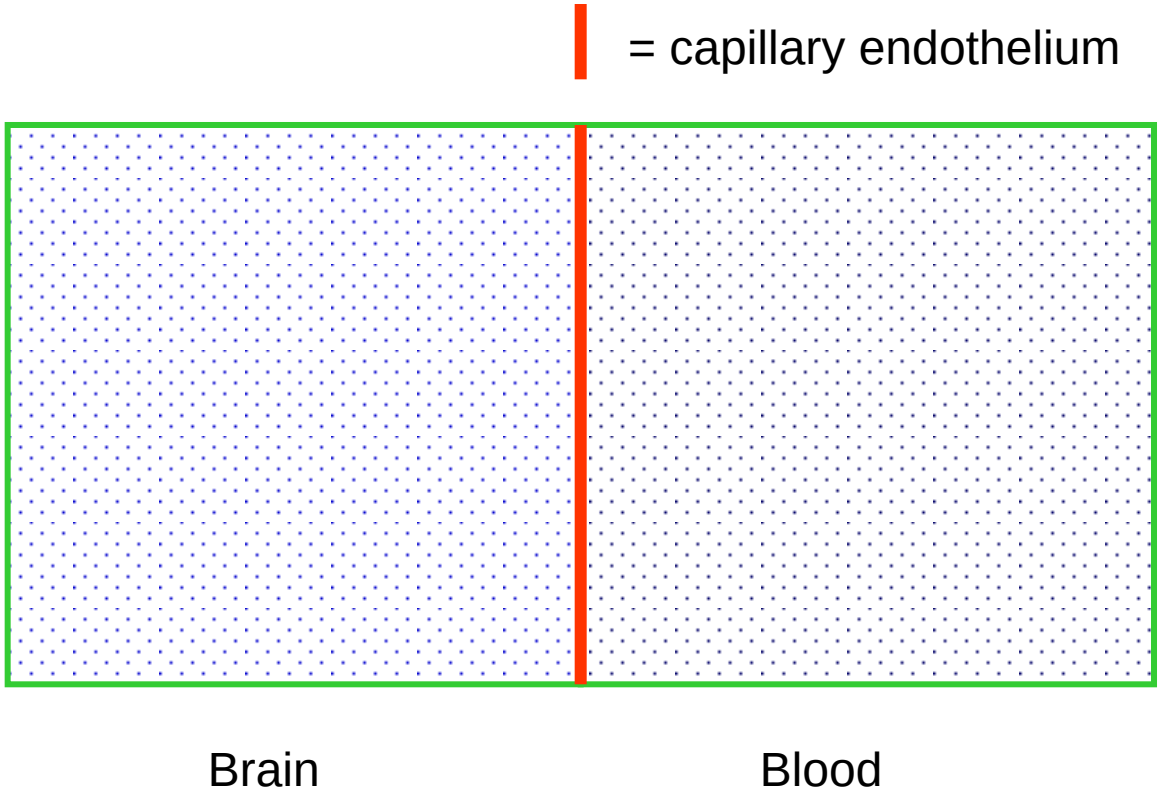


Fig. 8. Time courses of [^{3}H]PAH in the ipsilateral cerebrum after intracerebral microinjection in the presence of [^{14}C]inulin. The time courses of the percentage of [^{3}H]PAH remaining in the brain after administration in the absence (●) and presence (○) of 100 mM PAH (n=3–7). From Kakee et al. [61].

p-Aminohippuric acid (PAH)

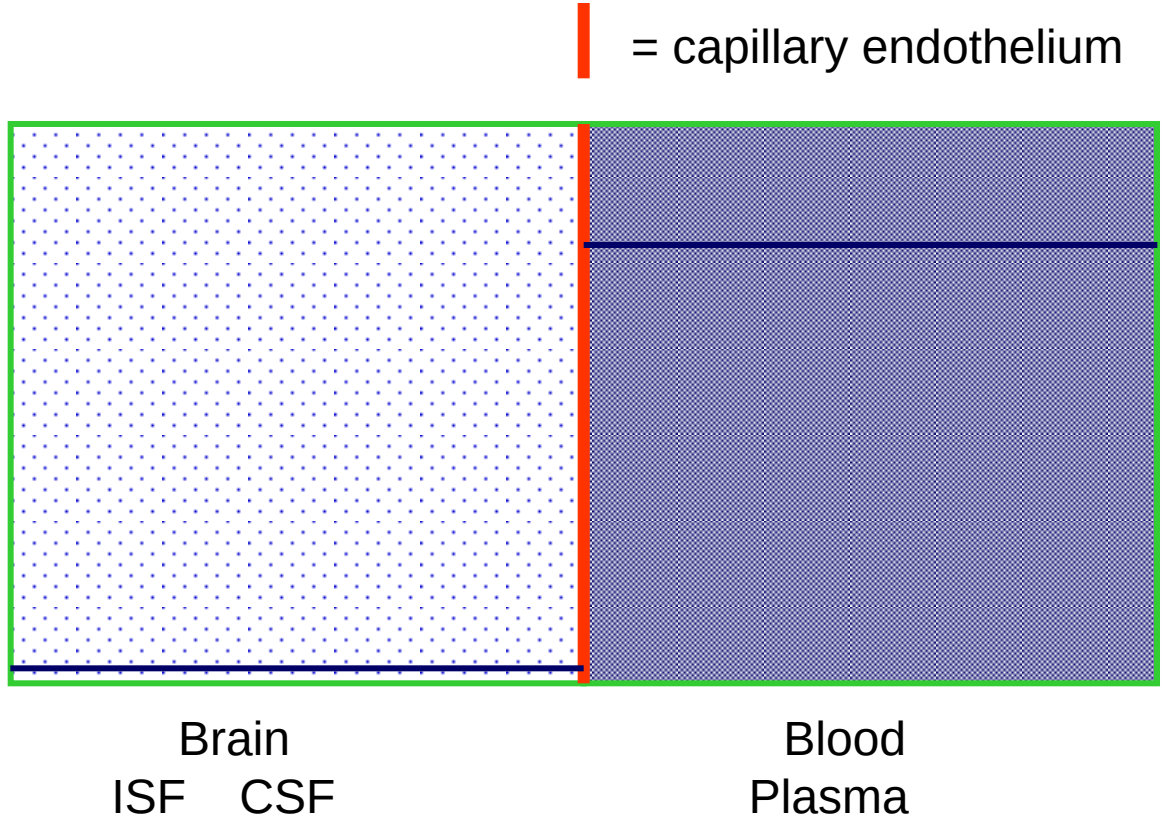
Brain water and protein concentration



The BBB is the only membrane that separates the brain from the blood

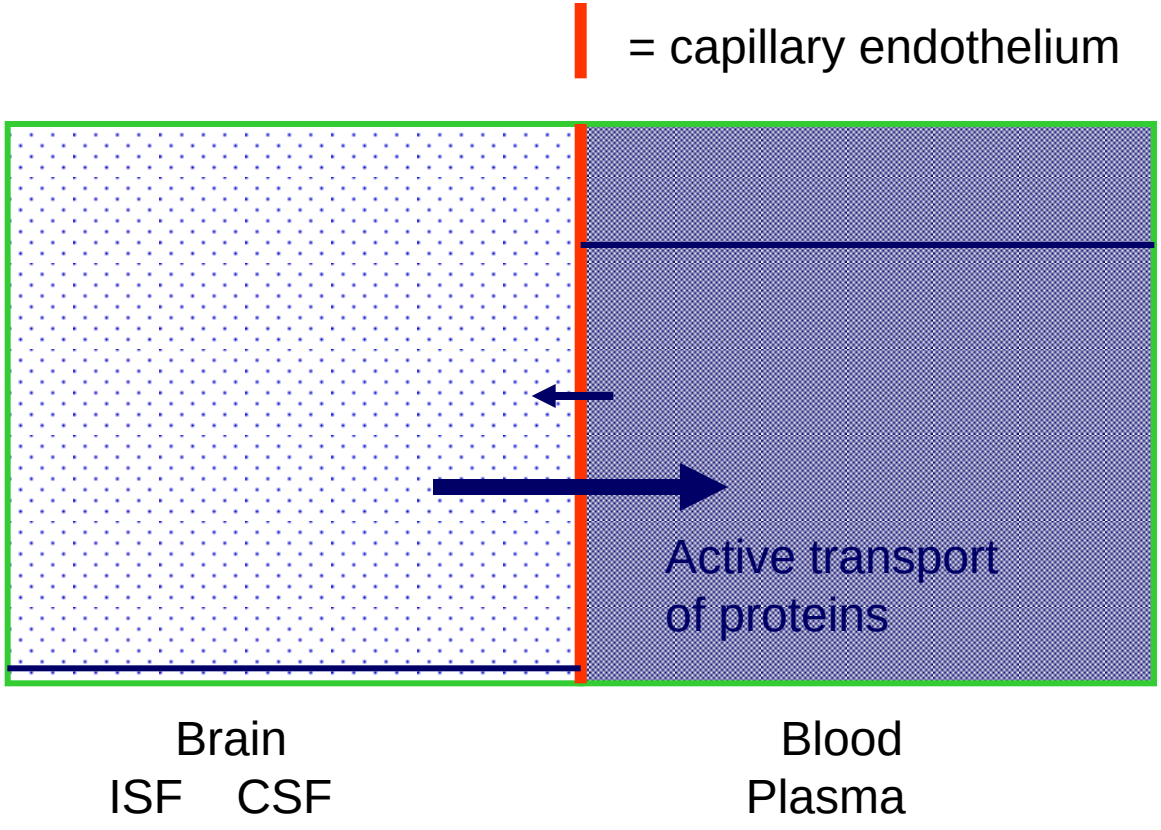
Brain water and protein concentration

Protein concentration in plasma is 200 times higher than in CSF



Brain water and protein concentration

Protein concentration in plasma is 200 times higher than in CSF



The low protein concentration in the CSF and ISF is maintained by active transport

Further evidence of rapid transport and rapid absorption in brain tissue

Intracerebral transport of HRP

10 min post intracisternal injection !!

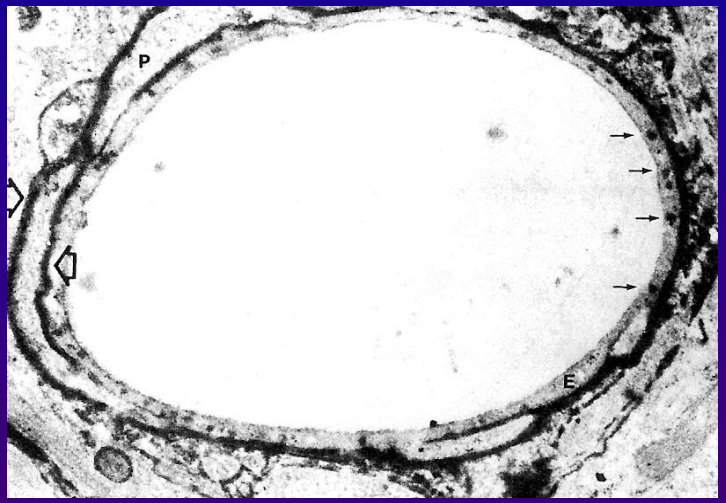
Frontal section of rat brain

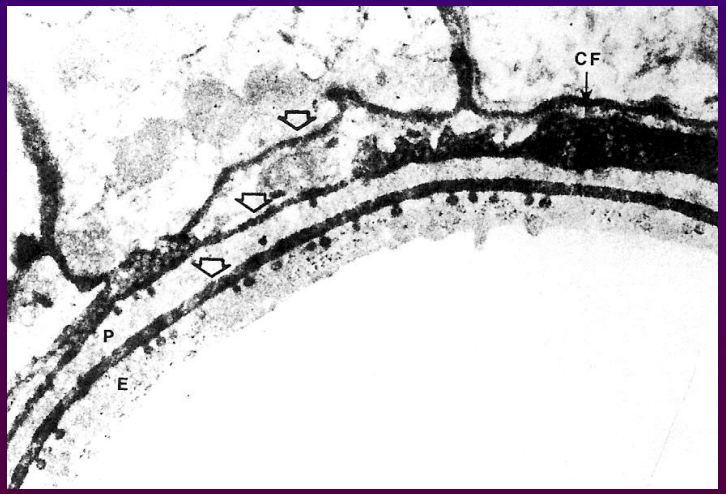
Artery W-R space

Wagner: Acta Neuropathol 1974

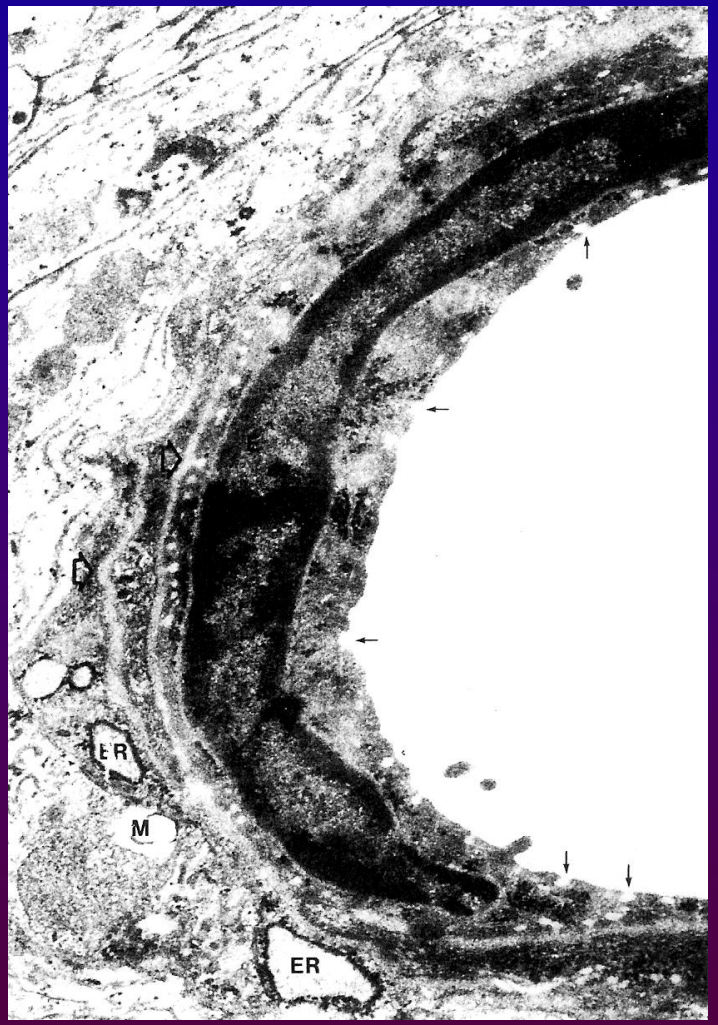
Capillary absorption of HRP

1h





24h triple dose



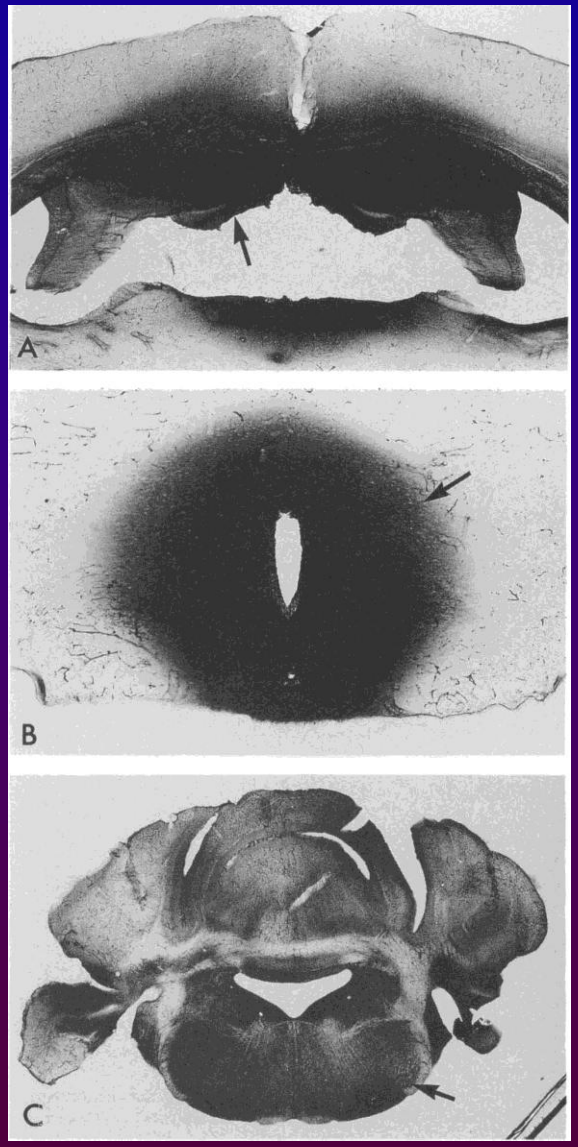
Capillary after intracisternal injection

Wagner: Acta Neuropathol 1974

Intracerebral transport of HRP after intraventricular injection in mice

5 min postinjection

4 h postinjection



Banks & Broadwell: J Neurochem 1994

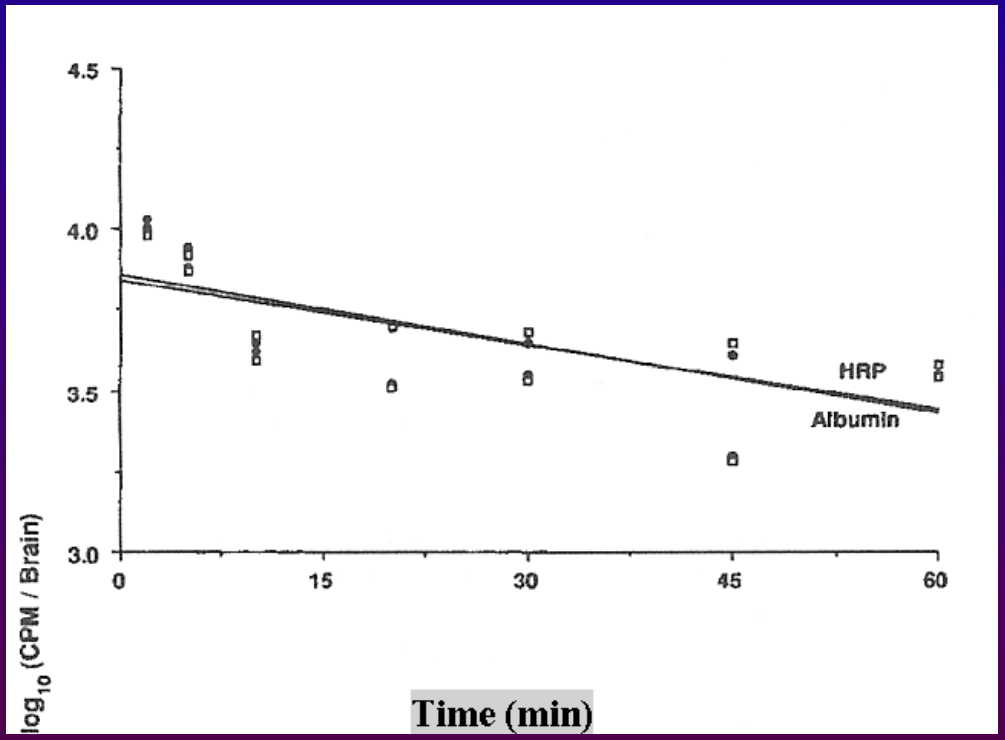
Brain to blood efflux of HRP and albumin after intraventricular injection

Half-time disappearance

from brain:

44 min for HRP

42 min for albumin



Brain concentration curve

Banks & Broadwell: J Neurochem 1994

Thus:
macromolecules are actively absorbed by the capillaries

To sum up:

- The CSF is absorbed by the brain capillaries
- Water-soluble molecules in the CSF are actively absorbed by the brain capillaries

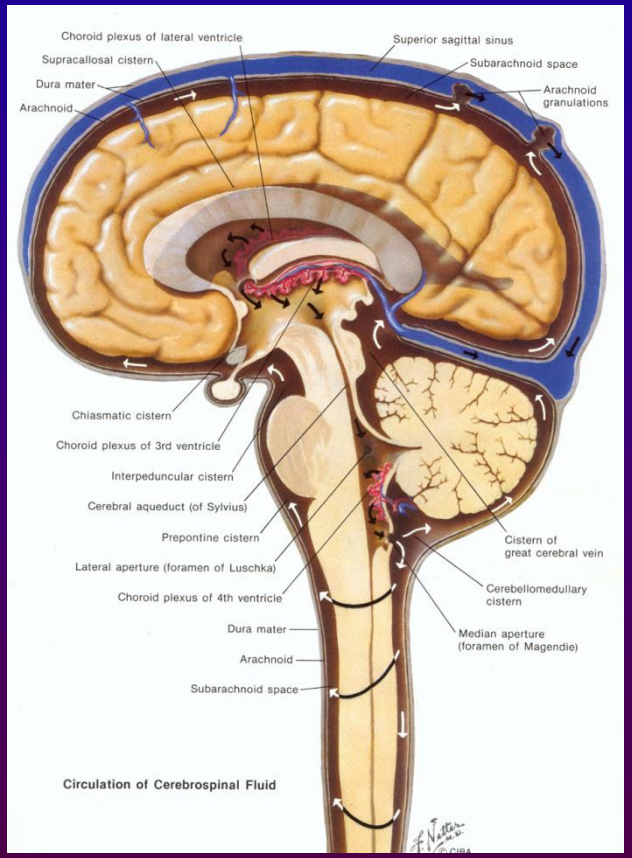
New Concept of CSF Circulation

1. CSF absorption by brain capillaries

2. **CSF production by brain capillaries**

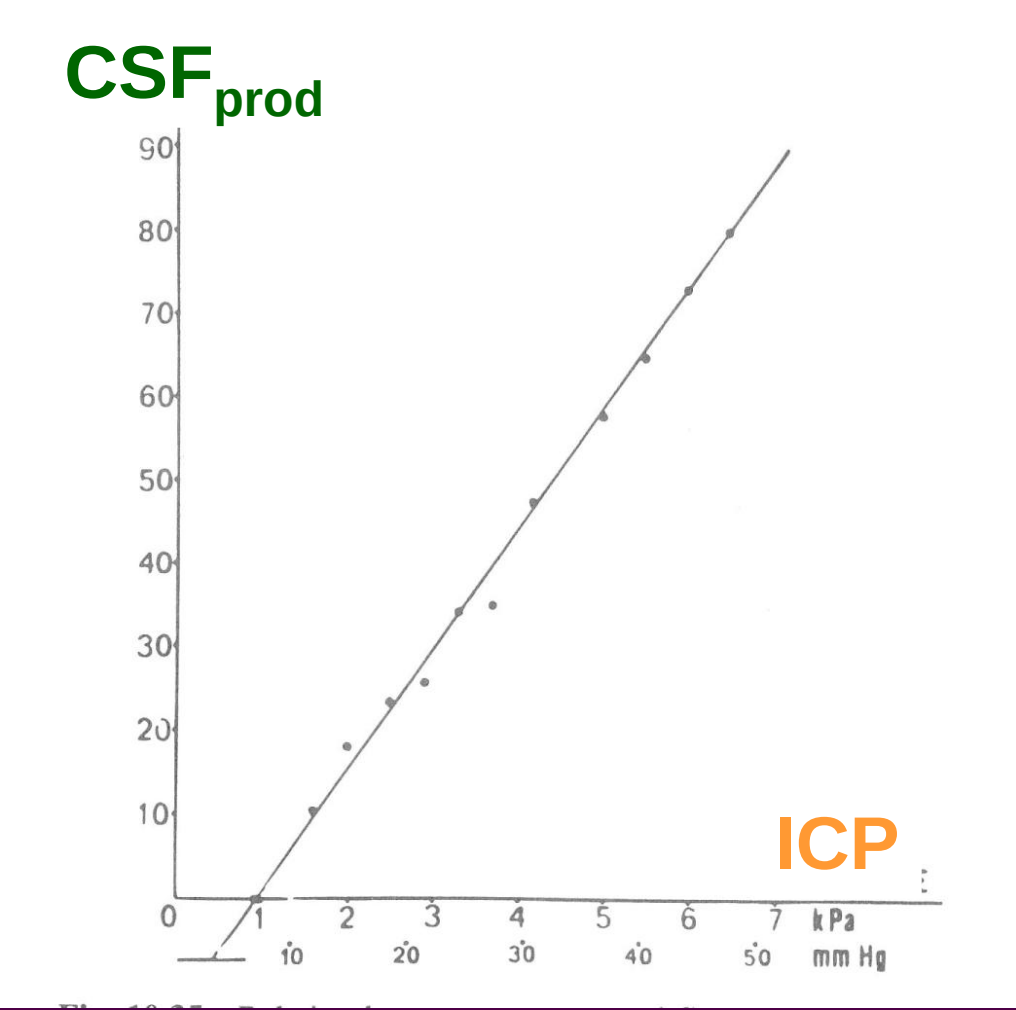
The CSF bulk flow model

is based on the assumption that the major part of the intracranial fluid is formed by the choroid plexus and that –



there is no fluid production in the brain capillaries !

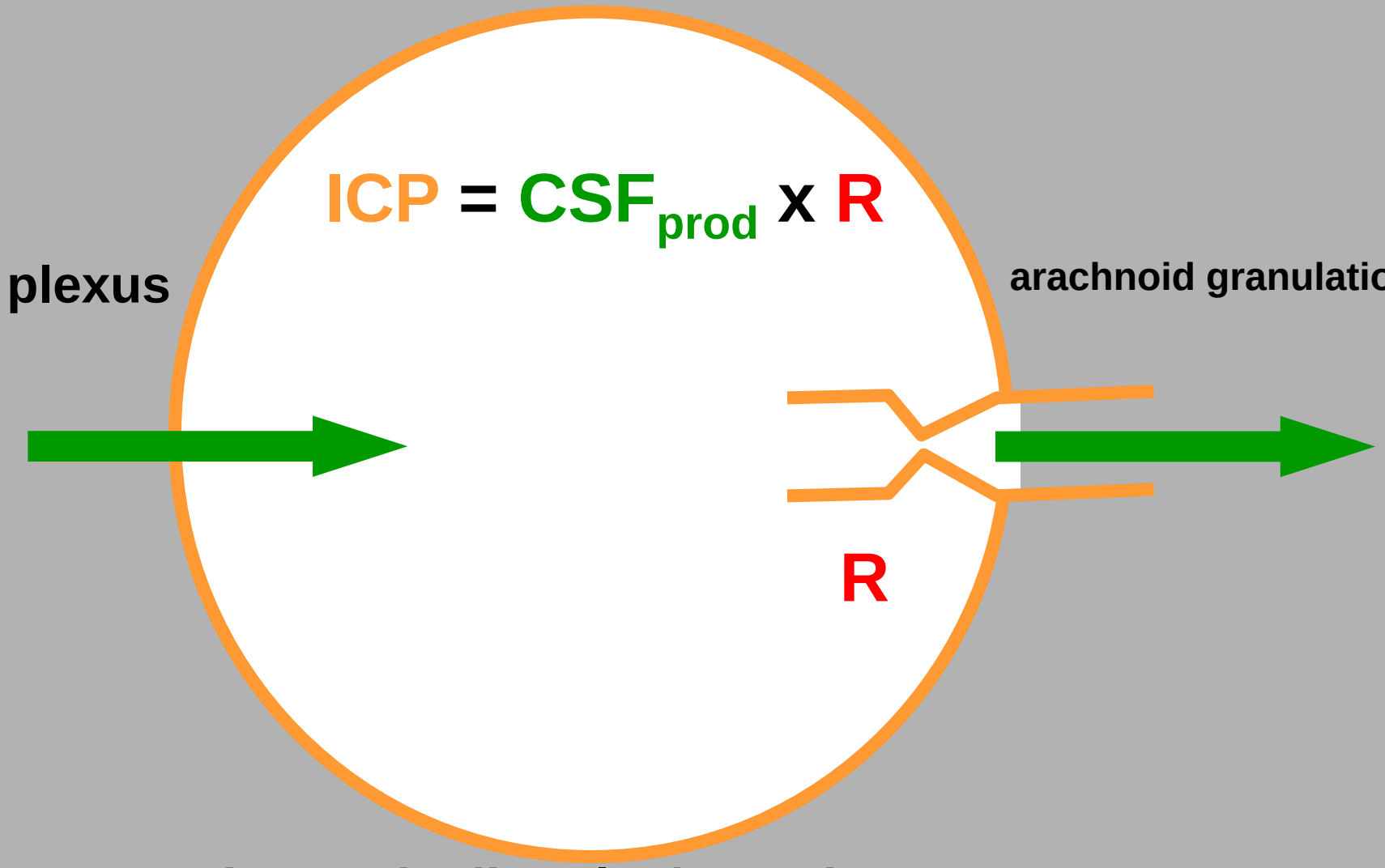
CSF infusion tests in healthy volunteers



Linear relation between CSF production and intracranial pressure (ICP)

Ekstedt 1975

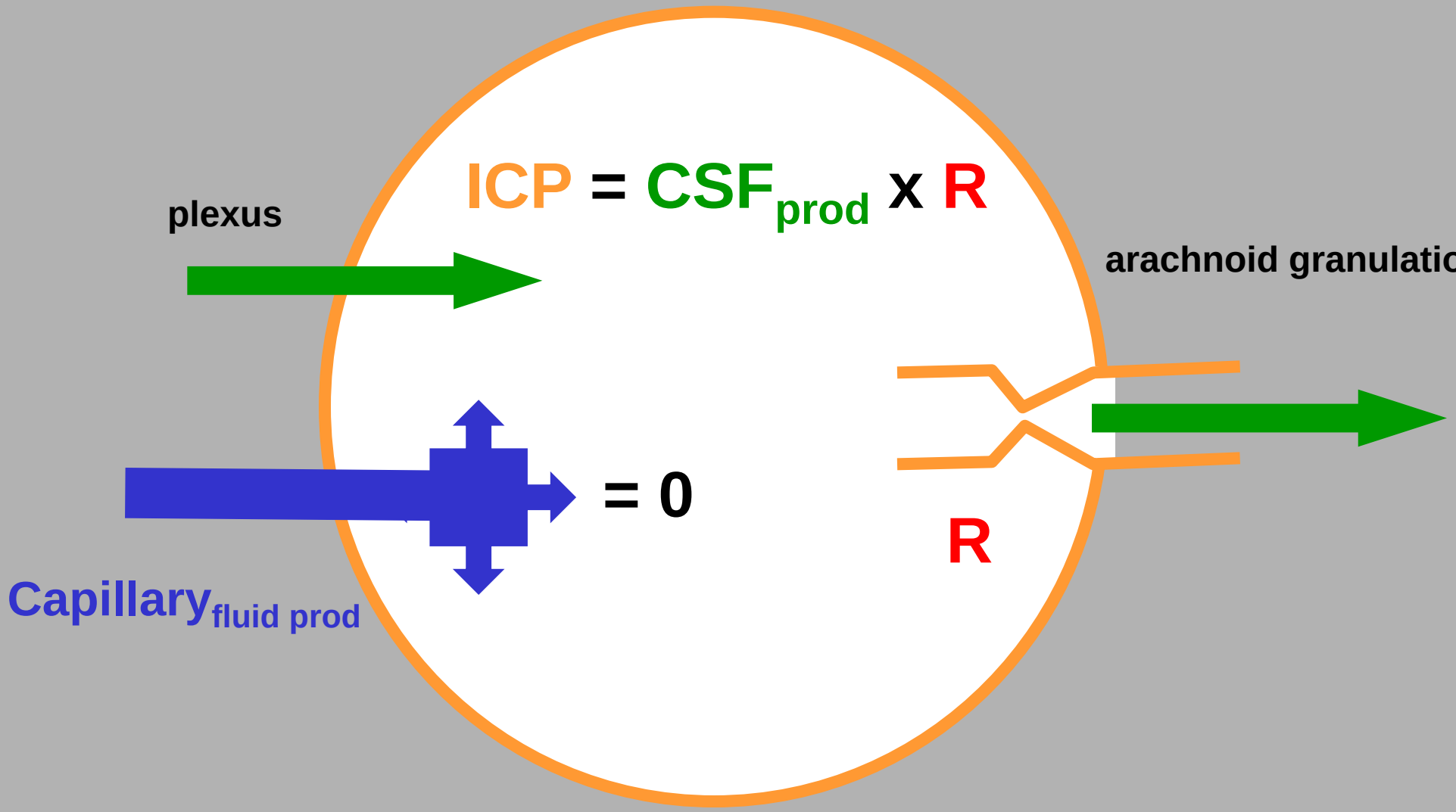
Intracranial pressure (ICP)



The ICP is directly dependent on

the CSF production in choroid plexus

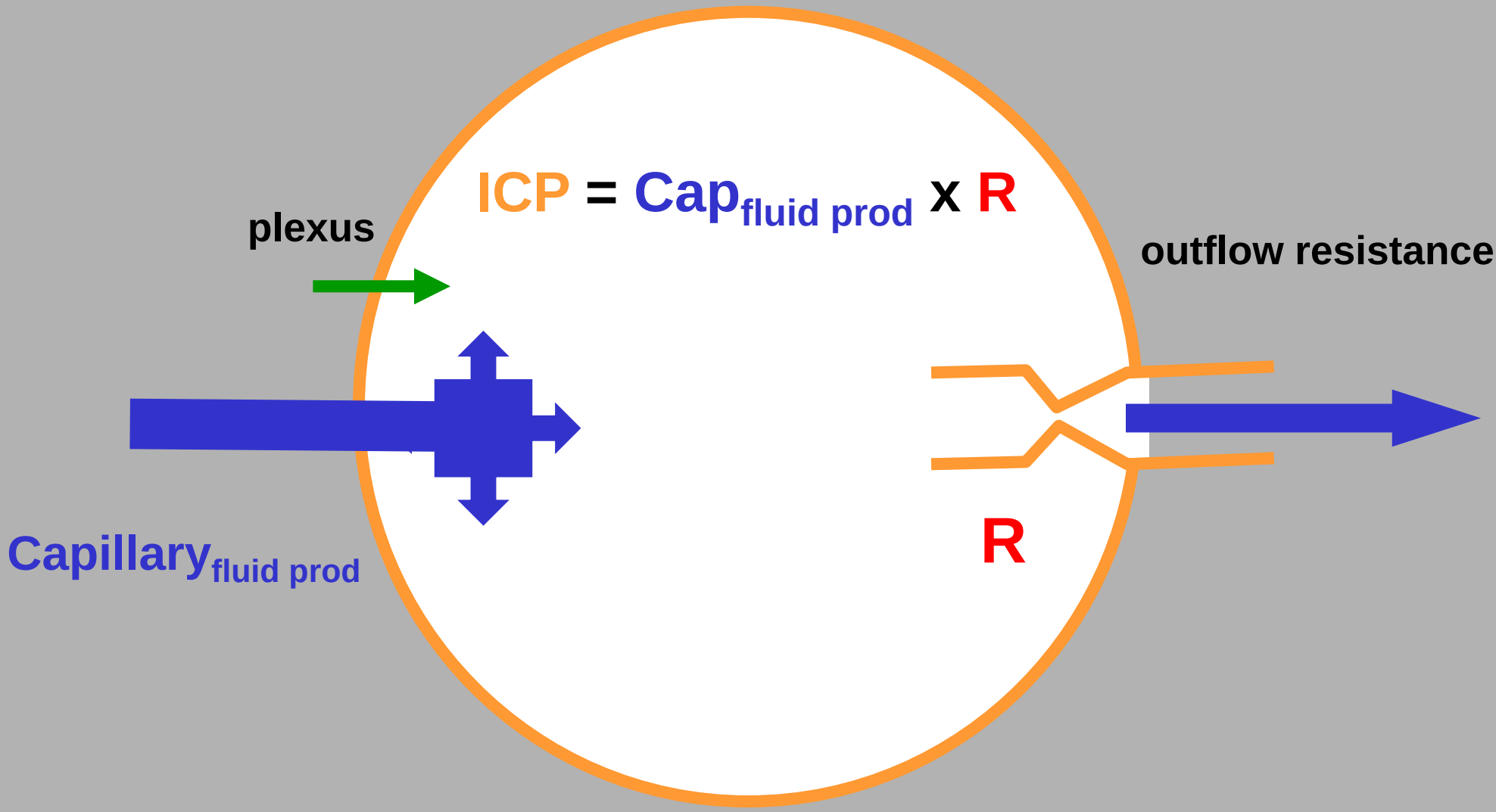
Intracranial pressure (ICP)



The bulk flow theory is based on assumption that -

there is no fluid production in the capillaries!

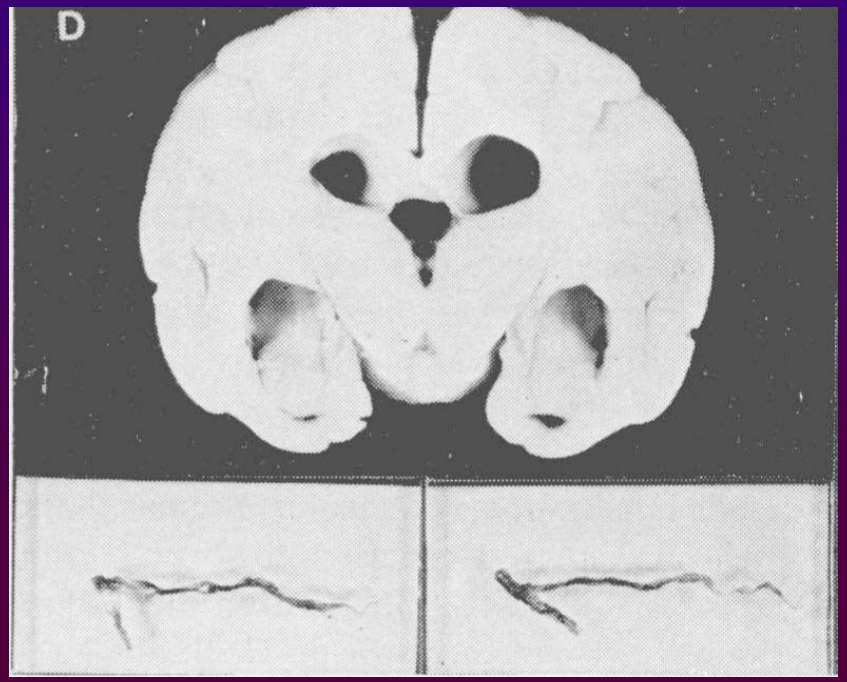
Intracranial pressure (ICP)



If the fluid production in the capillary is significant –

the ICP instead must be dependent on this production!

How much of the CSF formation is produced by the choroid plexus?

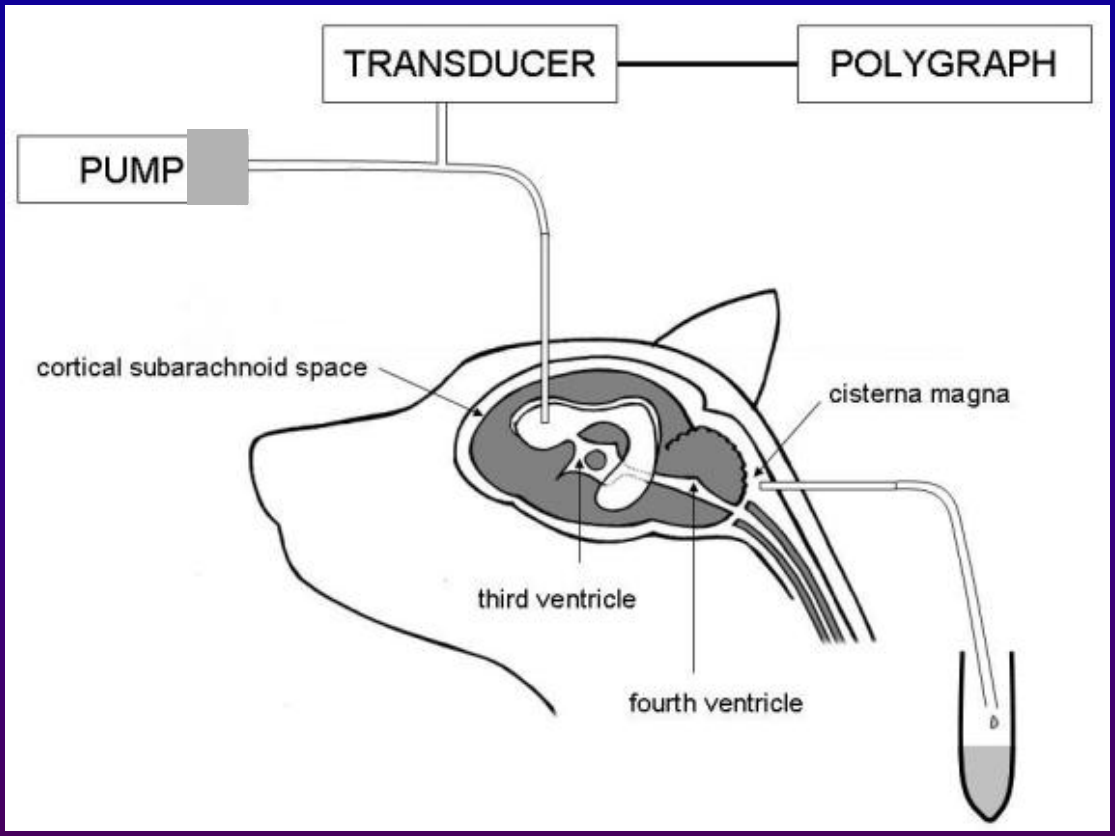


Experimental hydrocephalus in monkeys with and without plexectomy

Ion	Content in 14 normal animals	Content in 16 plexecto-mized animals
Na^{+}	158	156
K^{+}	2.8	2.7
Cl^{-}	132	129
Ca^{2+}	4.9	5.0
PO_4^{2-}	1.4	1.6
Mg^{2+}	3.5	3.8
Protein	18.1	18.2

Milhorat Science 1969

Measurement of CSF formation



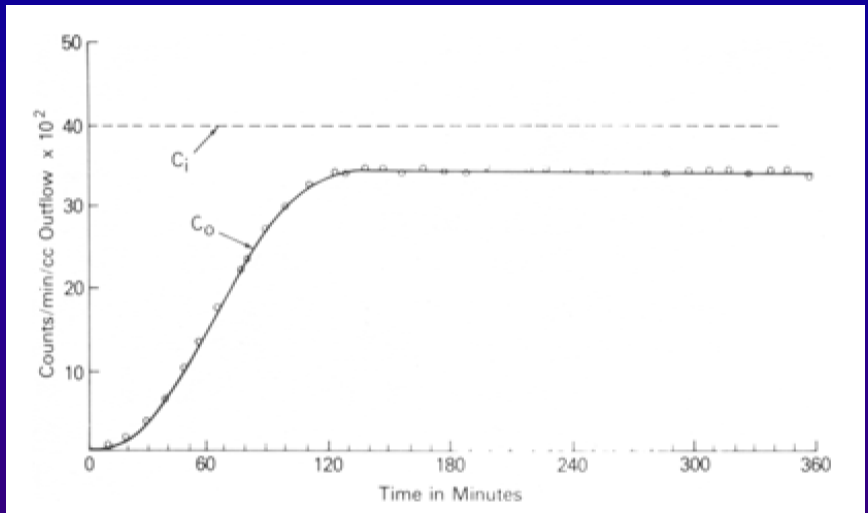
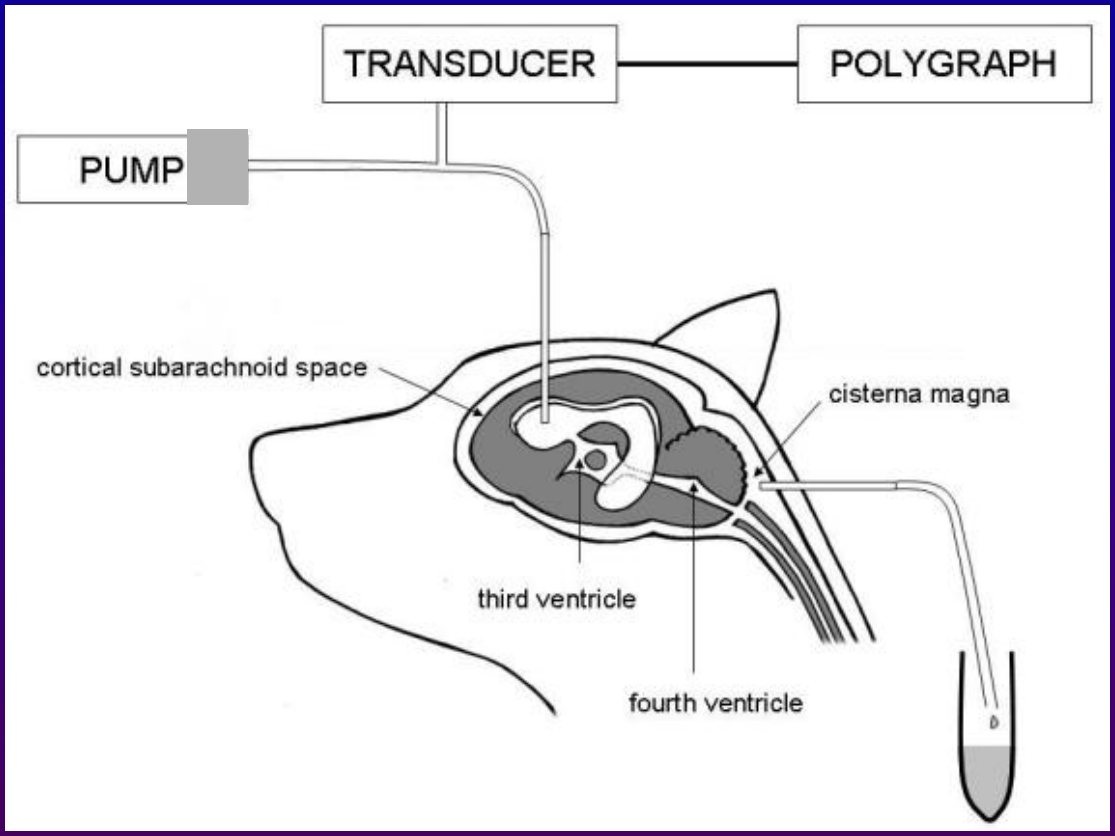


FIG. 4. Counts of ^{131}I albumin in influent (C_i)

- Infusion with a CSF tracer of known concentration and inflow rate
- With no CSF formation the outflow concentration equals inflow concentration

Measurement of CSF formation



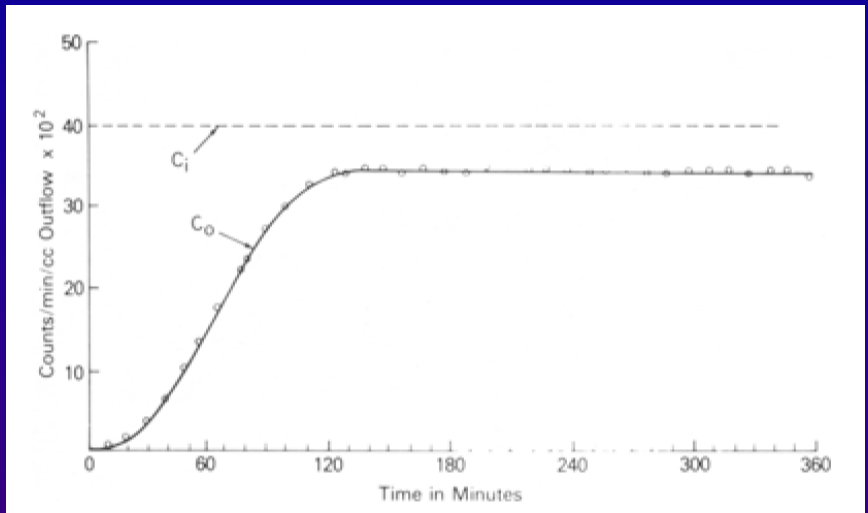


FIG. 4. Counts of ^{131}I albumin in influent (C_i)

- With CSF formation, there is dilution in the outflow concentration
- CSF prod = inflow rate x dilution in %

dilution = (inflow conc – outflow conc) / outflow conc

CSF production

Subarachnoid CSF production:

(red arrows)

60 % of total CSF production is produced in the subarachnoid space

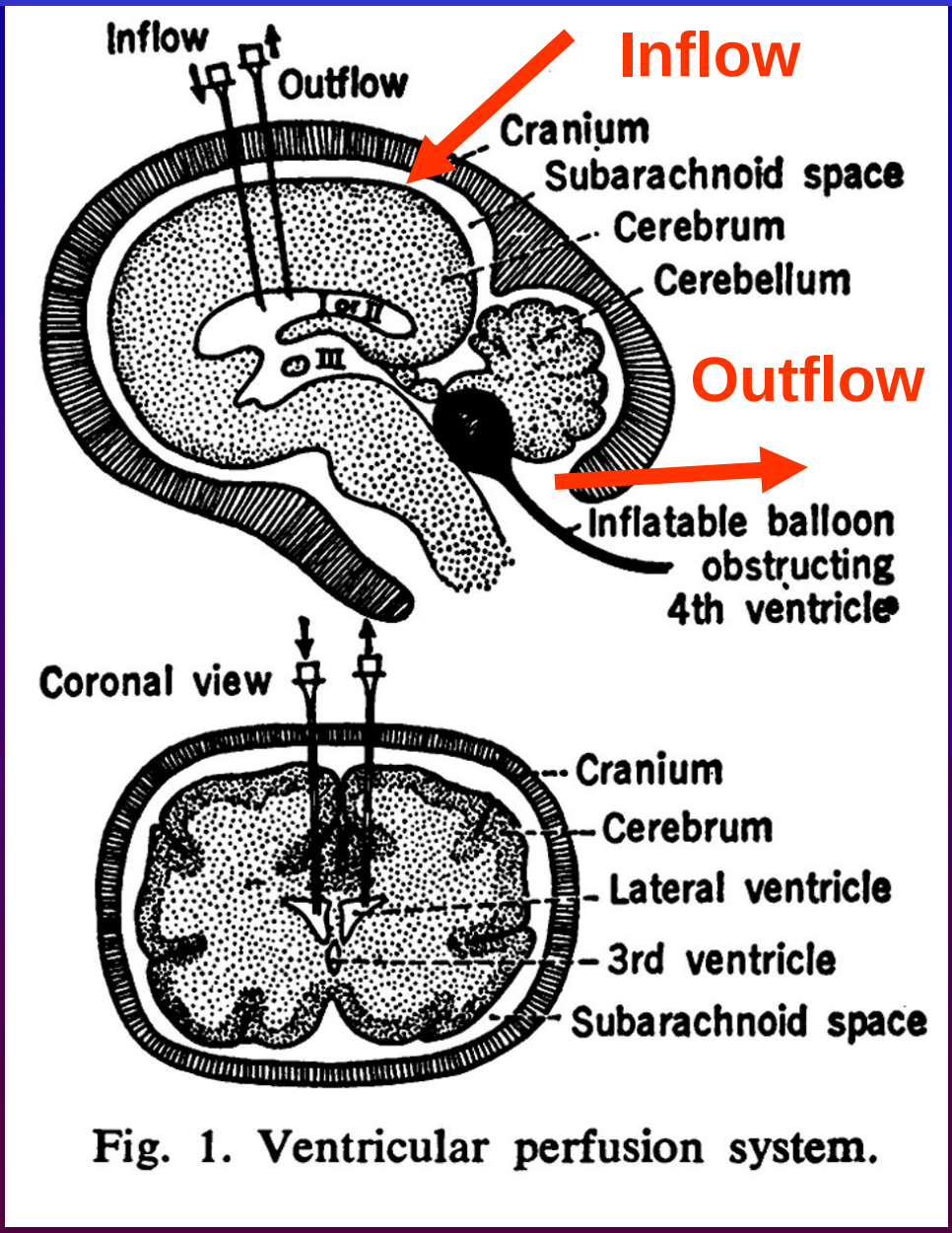


Fig. 1. Ventricular perfusion system.

Sato Bering 1965

CSF production

Subarachnoid CSF production:

(red arrows)

60 % of total CSF production is produced in the subarachnoid space

Ventricular CSF production:

(via 2 ventricular needles)

Only 40 % of total CSF production is produced in the ventricular system

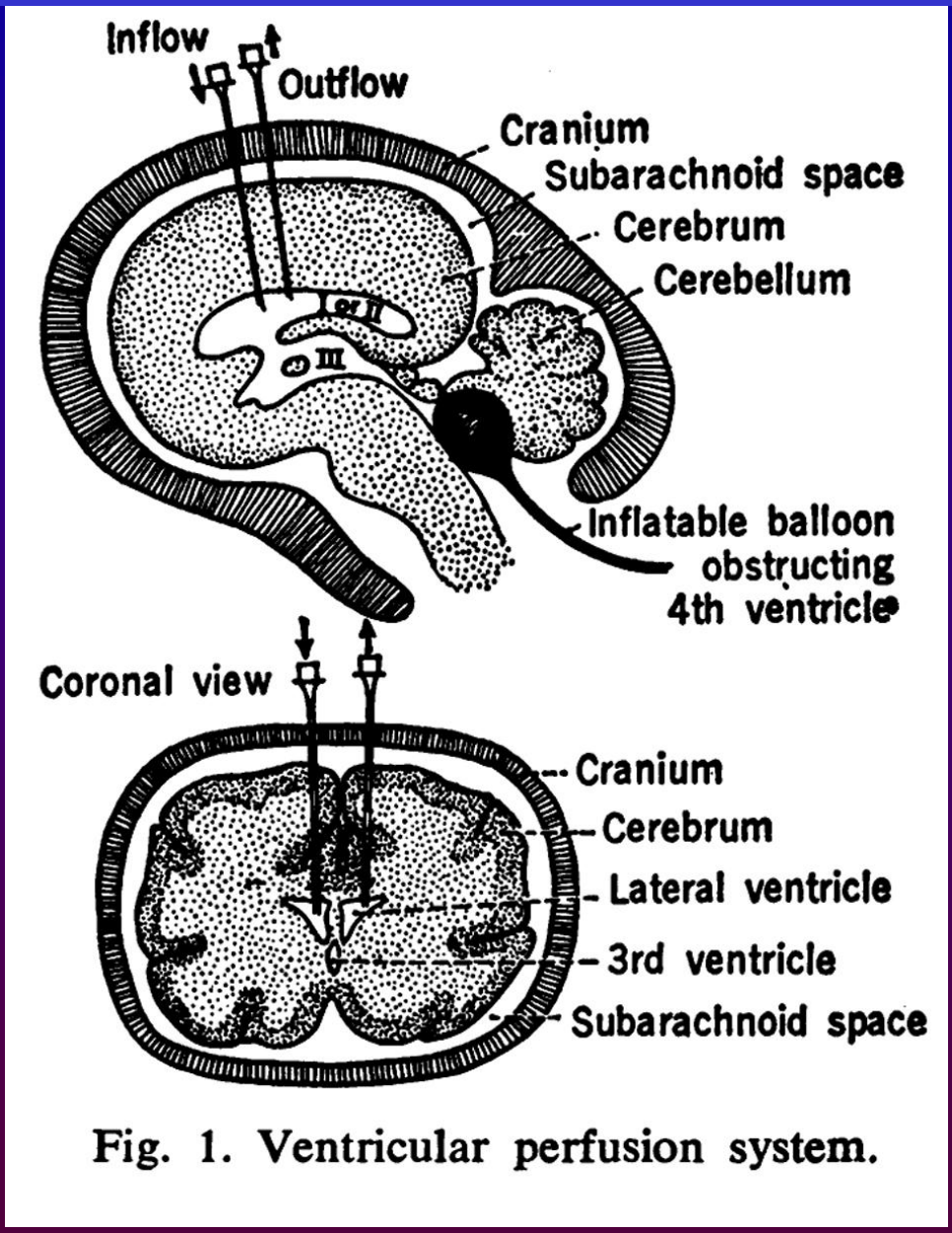


Fig. 1. Ventricular perfusion system.

Sato Bering 1965

CSF production after plexectomy

Ventricular CSF production:

Only 40 % of total CSF is produced in the ventricular system

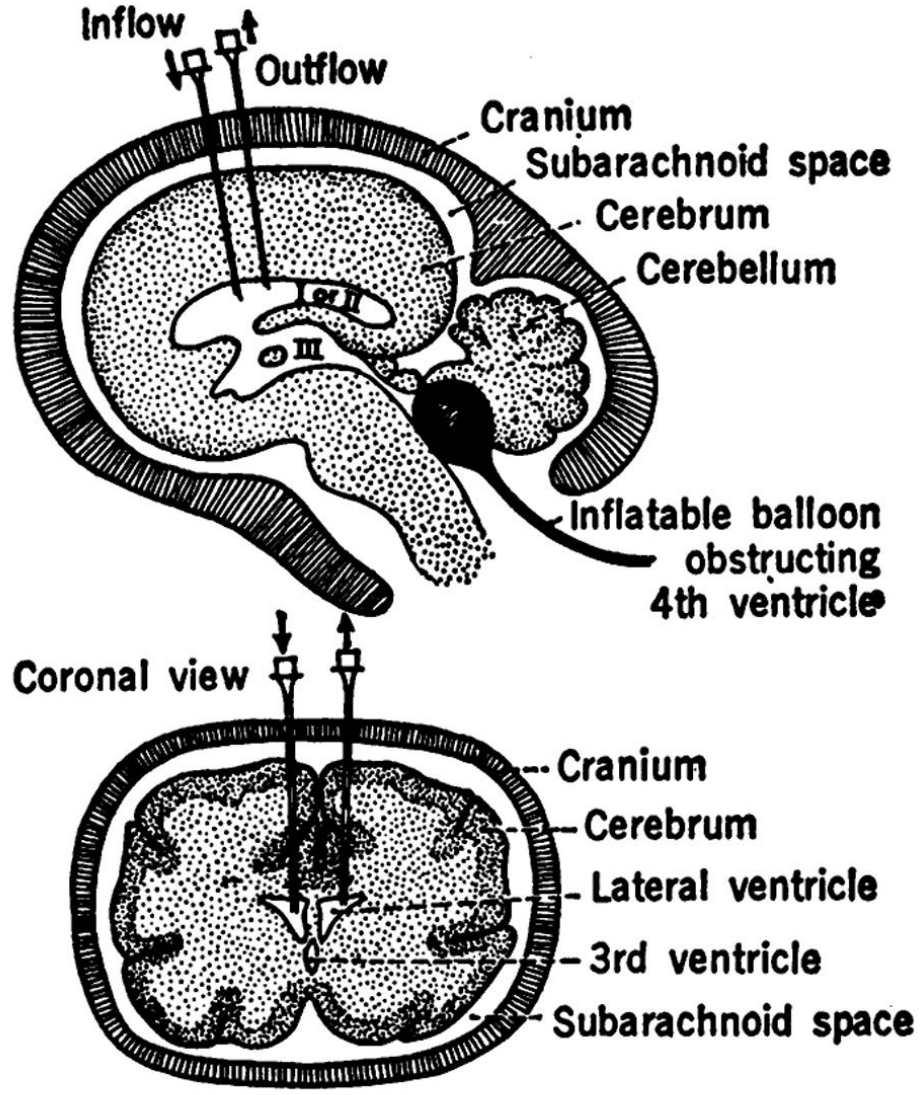


Fig. 1. Ventricular perfusion system.

Milhorat Science 1969

CSF production after plexectomy

Ventricular CSF production:

Only 40 % of total CSF is produced in the ventricular system

Ventricular CSF prod. after plexectomy:

Only 30% of the ventricular CSF is produced in the choroid plexus

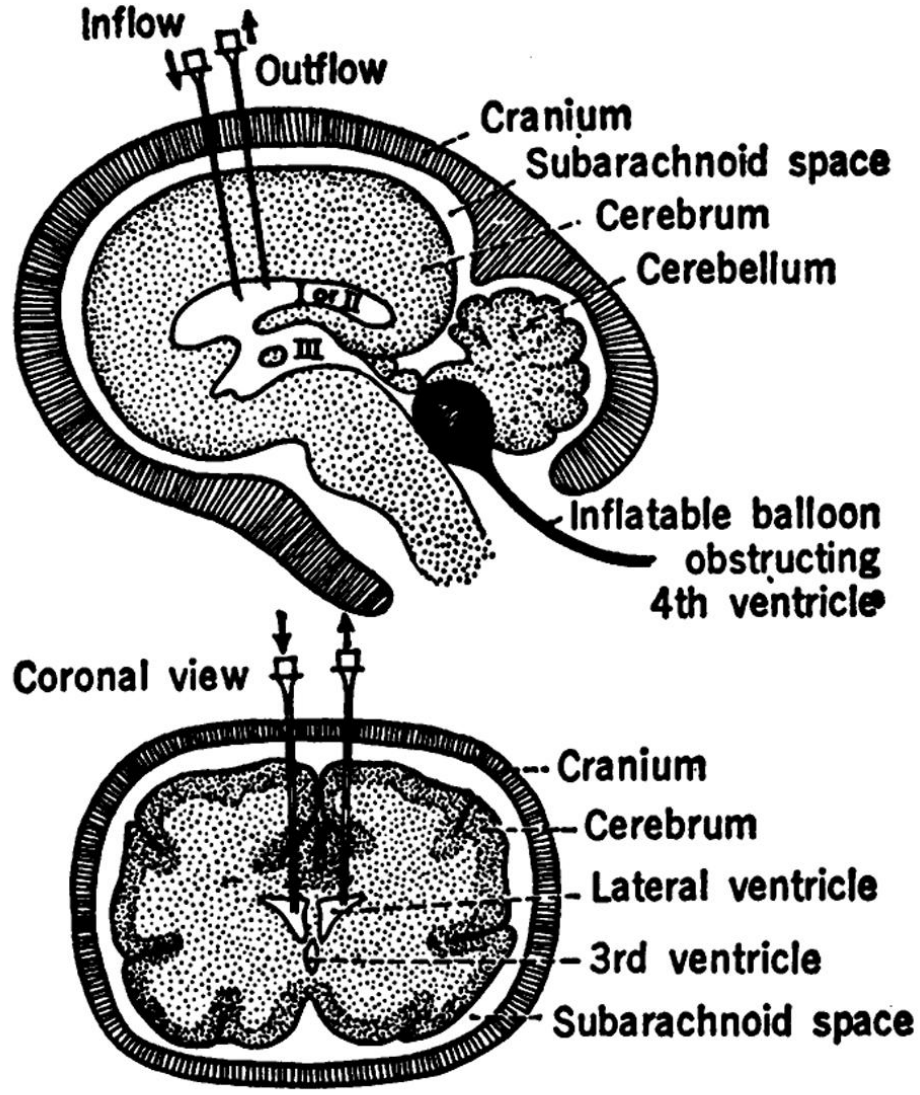


Fig. 1. Ventricular perfusion system.

Milhorat Science 1969

CSF production after plexectomy

Ventricular CSF production:

Only 40 % of total CSF is produced in the ventricular system

Ventricular CSF prod. after plexectomy:

Of the ventricular CSF production, only 30% is produced in the choroid plexus

This indicates that:
12% of the total CSF is produced by the choroid plexus

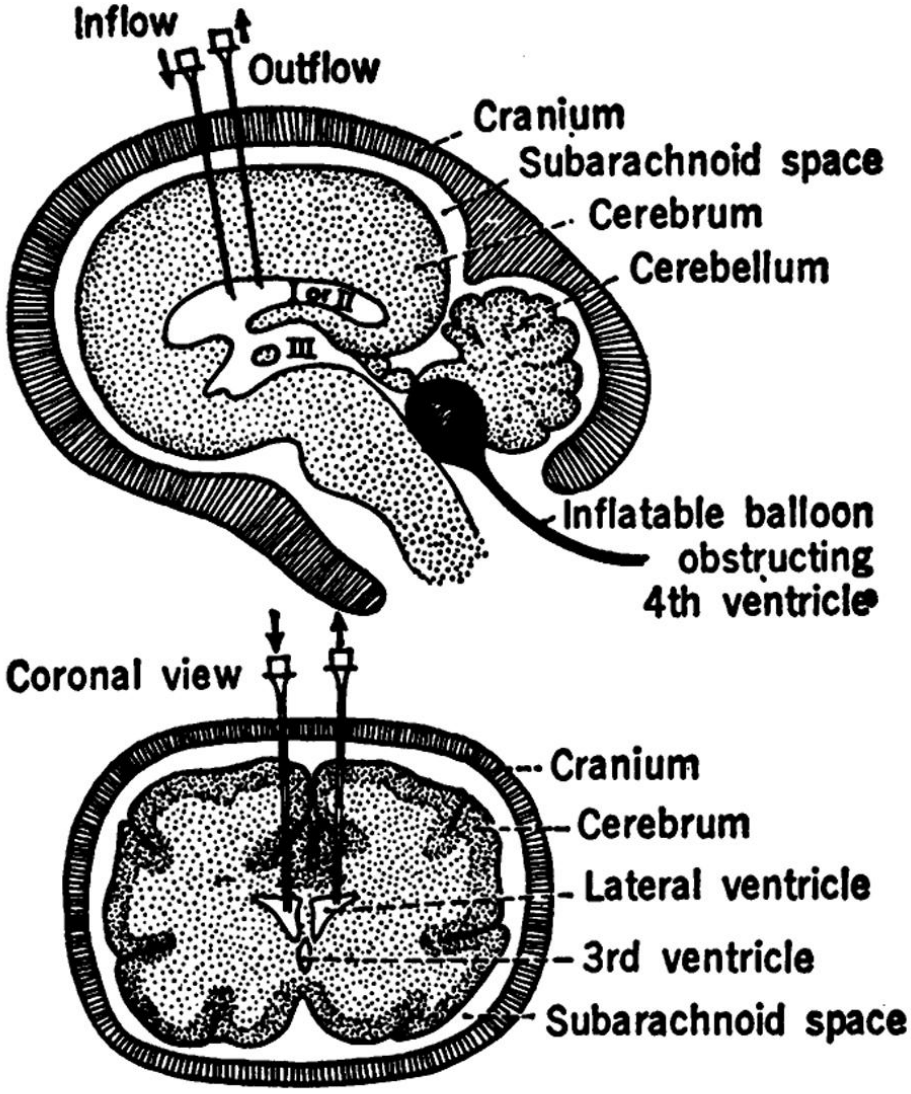


Fig. 1. Ventricular perfusion system.

Milhorat Science 1969

CSF production after plexectomy

Ventricular infusion without plexectomy:

Only 40 % of total CSF is produced in the ventricular system

Ventricular infusion after plexectomy:

Of the ventricular CSF production, only 30% is produced in the choroid plexus

Thus:

12% of the total CSF is produced by the choroid plexus

88% of the total CSF is produced by the brain capillaries

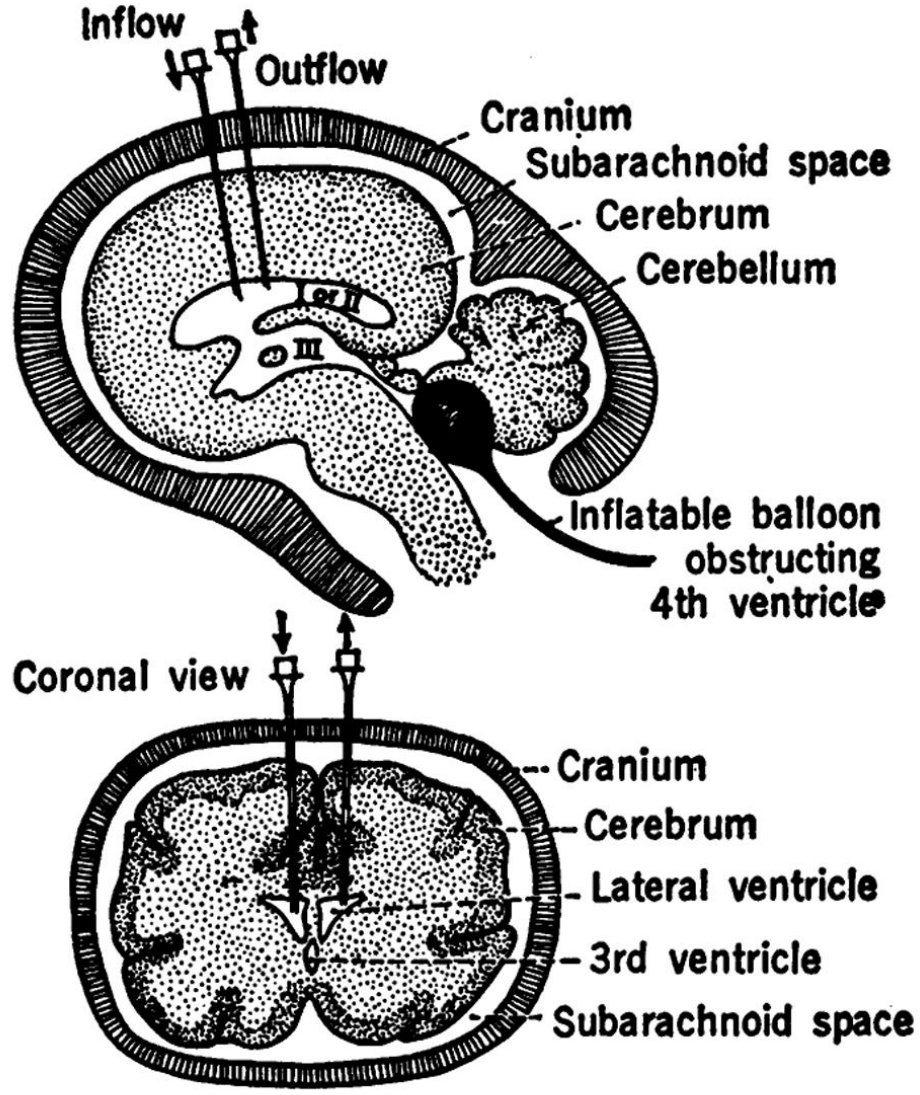
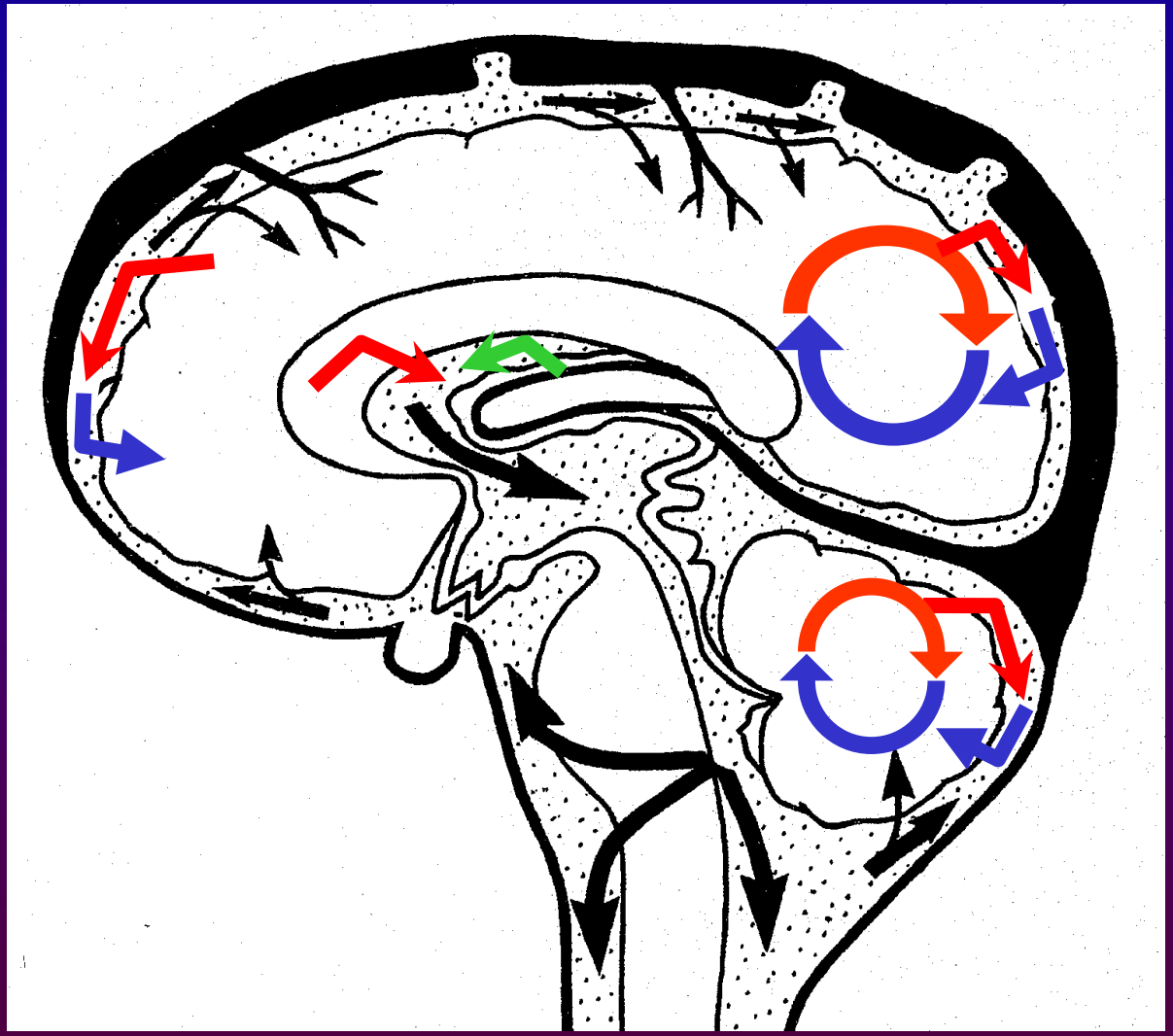


Fig. 1. Ventricular perfusion system.

Milhorat Science 1969

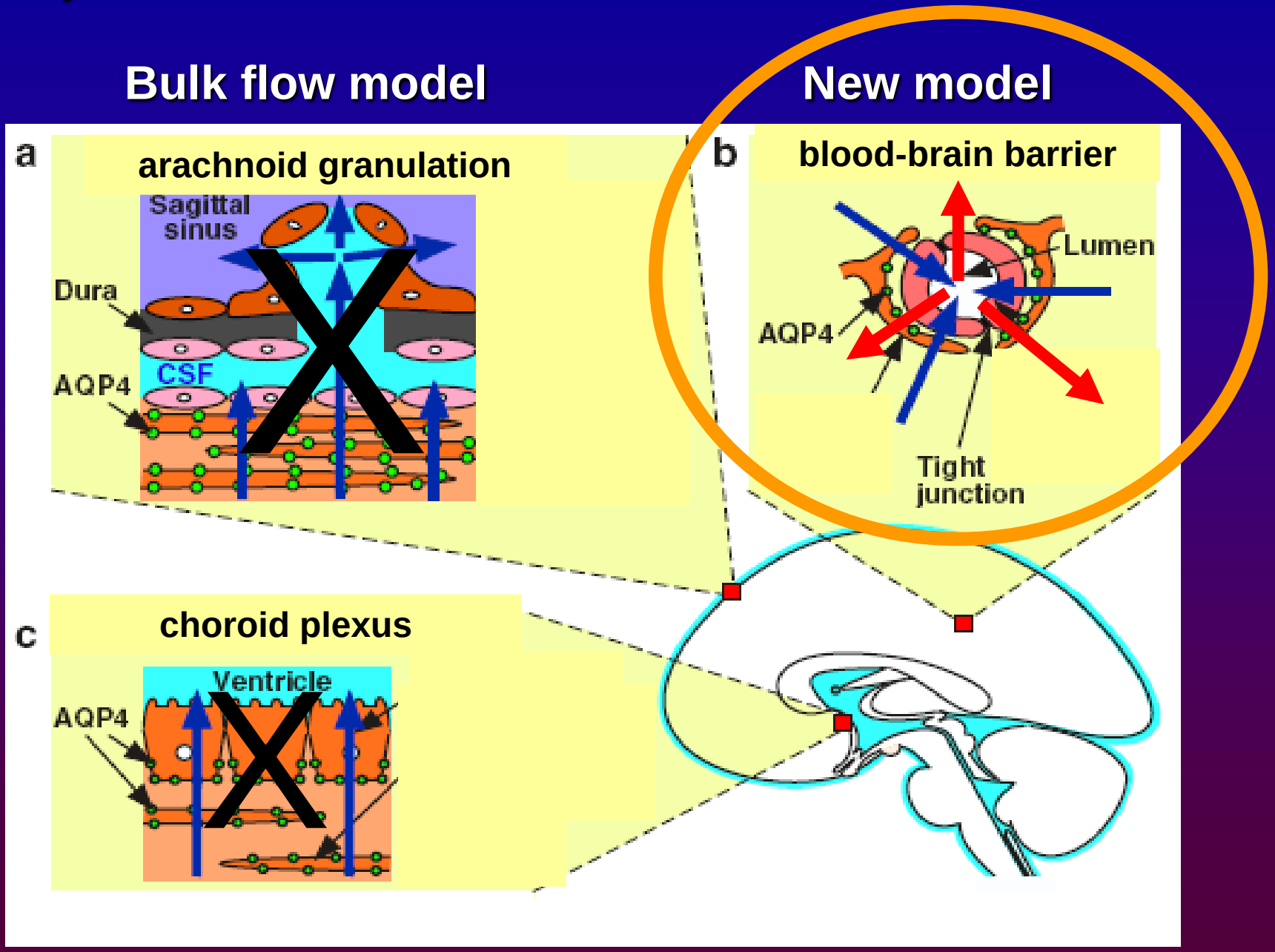
CSF production

New model



Only a minor part of the CSF is produced by the choroid plexus

Major route of water flow into and out of the brain



Conclusions

1. The major part of the CSF is produced and absorbed by the brain capillaries

2. Brain capillaries actively transport water-soluble molecules from the brain

3. Active transport from brain to blood is a prerequisite for brain homeostasis