Cerebral blood flow and metabolism – Lecture 1

For 3rd year Students of Medicine

Prof. Ferenc Bari

September 5, 2018

DEPARTMENT OF MEDICAL PHYSICS AND INFORMATICS
University of Szeged, Faculty of Medicine, Faculty of Science and Informatics

The aim of the course

An overview of cerebral circulation

- Important for normal vital functions;
- Disease states: disturbed cerebral circulation affects motor, intelectual and autonomic funtions
- Detection of (ab)normal cerebral circulation;
- Diagnostic tools

Speakers

- Prof. Ferenc Bari (Department of Medical Physics and Informatics)
- Dr. Ferenc Domoki (Department of Physiology)
- Dr. Tamás Kincses (Department of Neurology)
- Dr. Zoltán Ungvári (Reynolds Oklahoma Center on Aging Department of Geriatric Medicine University of Oklahoma Health Sciences Center)
- Dr. Eszter Farkas (Department of Medical Physics and Informatics)





Tentative structure of the course

English, Wednesday: 16:00-17:30		
Time	Topic	Lecturer
September 5, 2017	Introduction	Prof. Ferenc Bari
September 12, 2017	The blood brain barrier	Dr. Eszter Farkas
September 19, 2017	Physiology of the cerebral smooth muscle cell	Prof. Ferenc Bari
September 26, 2017	Regulation of cerebrovascular tone: the role of the endothelium	Prof. Ferenc Bari
October 3, 2017	Clinical neuroimaging	Dr. Tamás Kincses
October 10, 2017	Regulation of cerebrovascular tone: metabolic components	Dr. Ferenc Domoki
October 17, 2017	Neurovascular coupling	Dr. Eszter Farkas
October 24, 2017	Autumn break	
October 31, 2017	Regulation of cerebrovascular tone: neural components	Prof. Ferenc Bari
November 7, 2017	The regulation of the cerebral blood flow in the neonate	Dr. Ferenc Domoki
November 14, 2017	Students' Conference	
November 21, 2017	Aging and dementia	Dr. Zoltán Ungvári
November 28, 2017	Cerebral small vessel disease	Dr. Eszter Farkas
December 5, 2017	Written examination	Dr. Eszter Farkas

Content of the course

Is it too early (pathophysiology, pathology, internal medicine, radiology etc)?

Possibly, but

- you have basic knowledge (physiology, anatomy, biochemistry)
- you have motivation
- you can gain motivation

Content of the course

Is it too complex?

Possibly, but each part is exciting

Why take the course?

- Public health considerations (prevention, health education, rehabilitation etc)
- Basic science as well as applied science methods
- Just for some credit points? For some students, possibly – what can we do?

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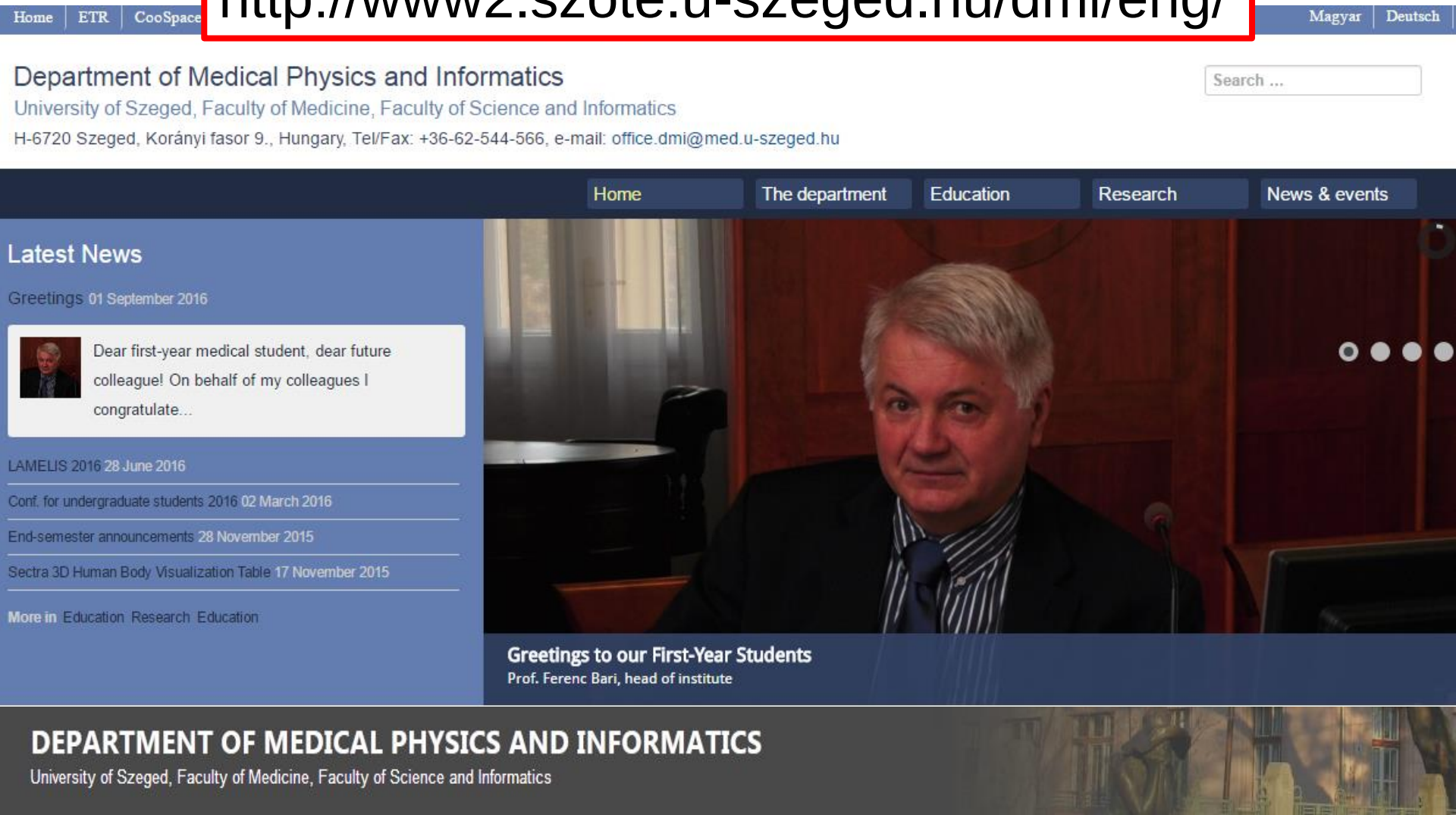
http://www2.szote.u-szeged.hu/dmi/eng/



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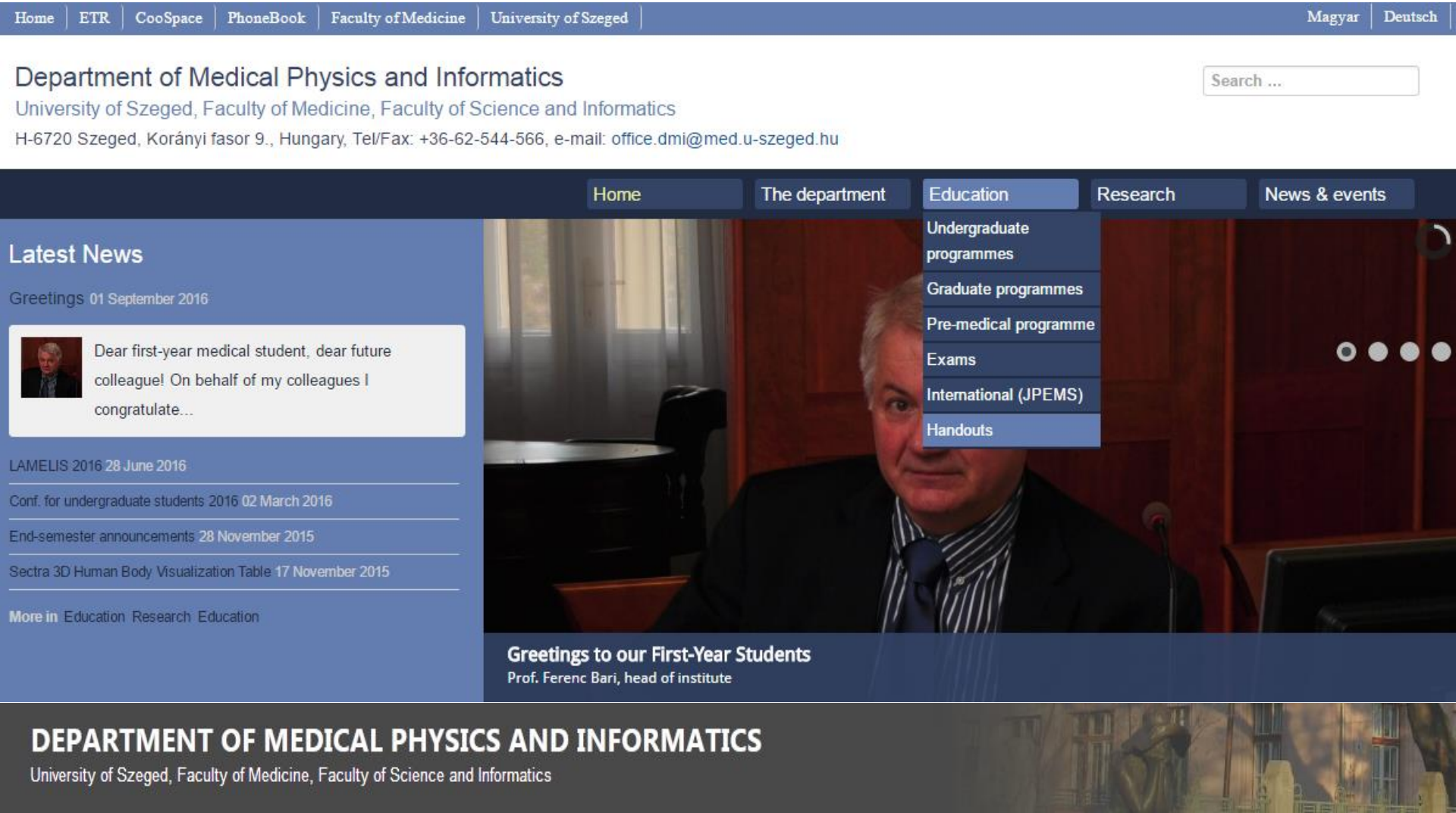

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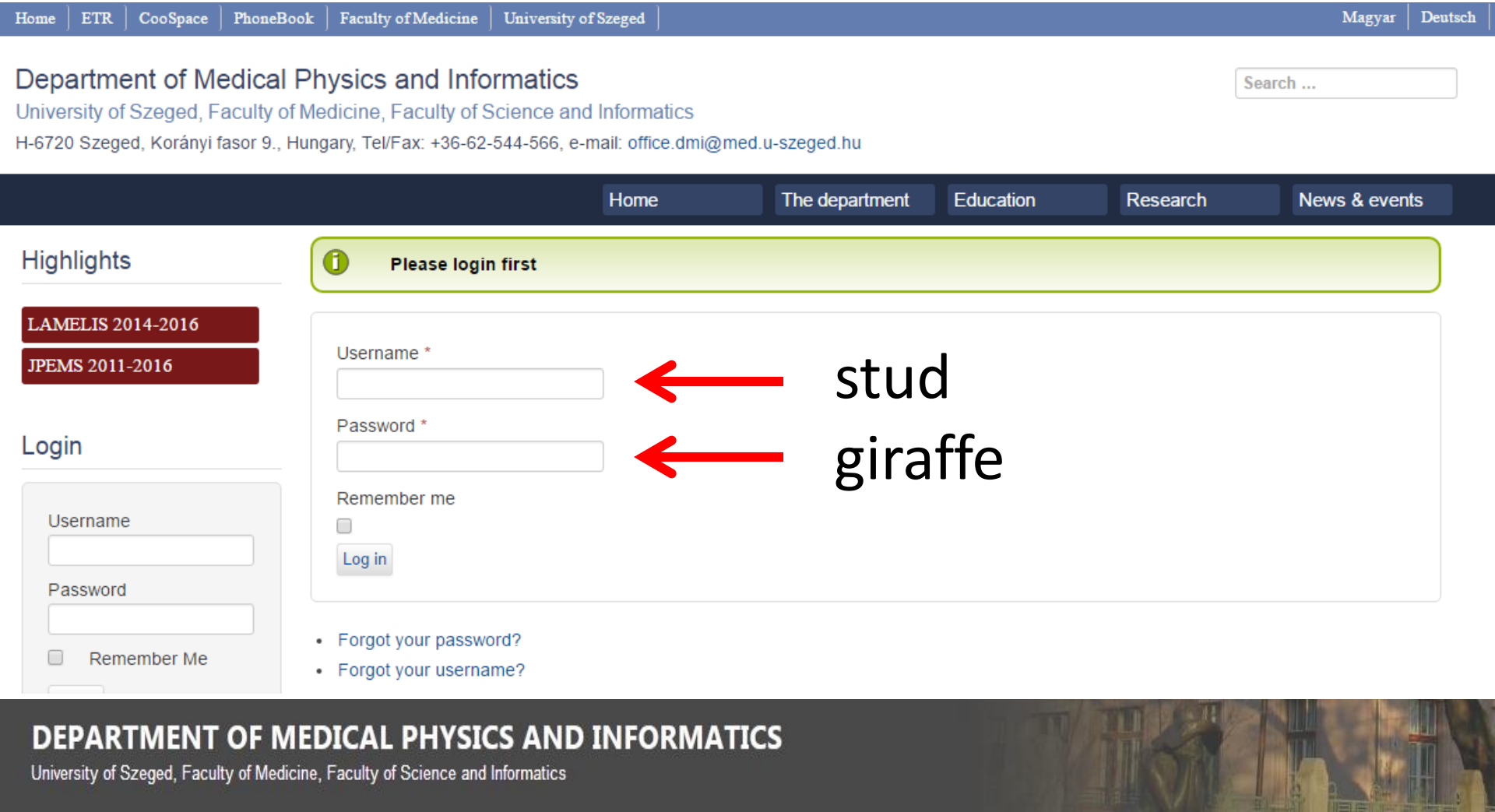

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Exam sample sheet

Formulas and tables

Biostatistical methods (manuscript - Dr. Krisztina Boda)

Faculty of Medicine - Cerebral blood flow and metabolism

Cerebral lecture 1 (Prof. Ferenc Bari)
Cerebral lecture 2 (Prof. Ferenc Bari)
Cerebral lecture 3 (Prof. Ferenc Bari)
Cerebral lecture 4 (Prof. Ferenc Bari)
Cerebral lecture 5 (Prof. Ferenc Bari)
Cerebral lecture 6 (Prof. Ferenc Bari)
Cerebral lecture 7 (Dr. Eszter Farkas)
Cerebral lecture 8 (Dr. Ferenc Domoki)
Cerebral lecture 9 (Prof. Ferenc Bari)
Cerebral lecture 10 (Dr. Ferenc Domoki)
Cerebral lecture 11 (Dr. Eszter Farkas)
Cerebral lecture 12 (Prof. Ferenc Bari)
Cerebral lecture 12 supplement (Prof. Ferenc Bari)
Cerebral lecture 13 (Dr. Eszter Farkas)

Cerebral blood flow supplement1

Handouts 2014/2015 (2nd semester)
Handouts 2014/2015 (1st semester)
Handouts 2013/2014 (2nd semester)
Handouts 2013/2014 (1st semester)

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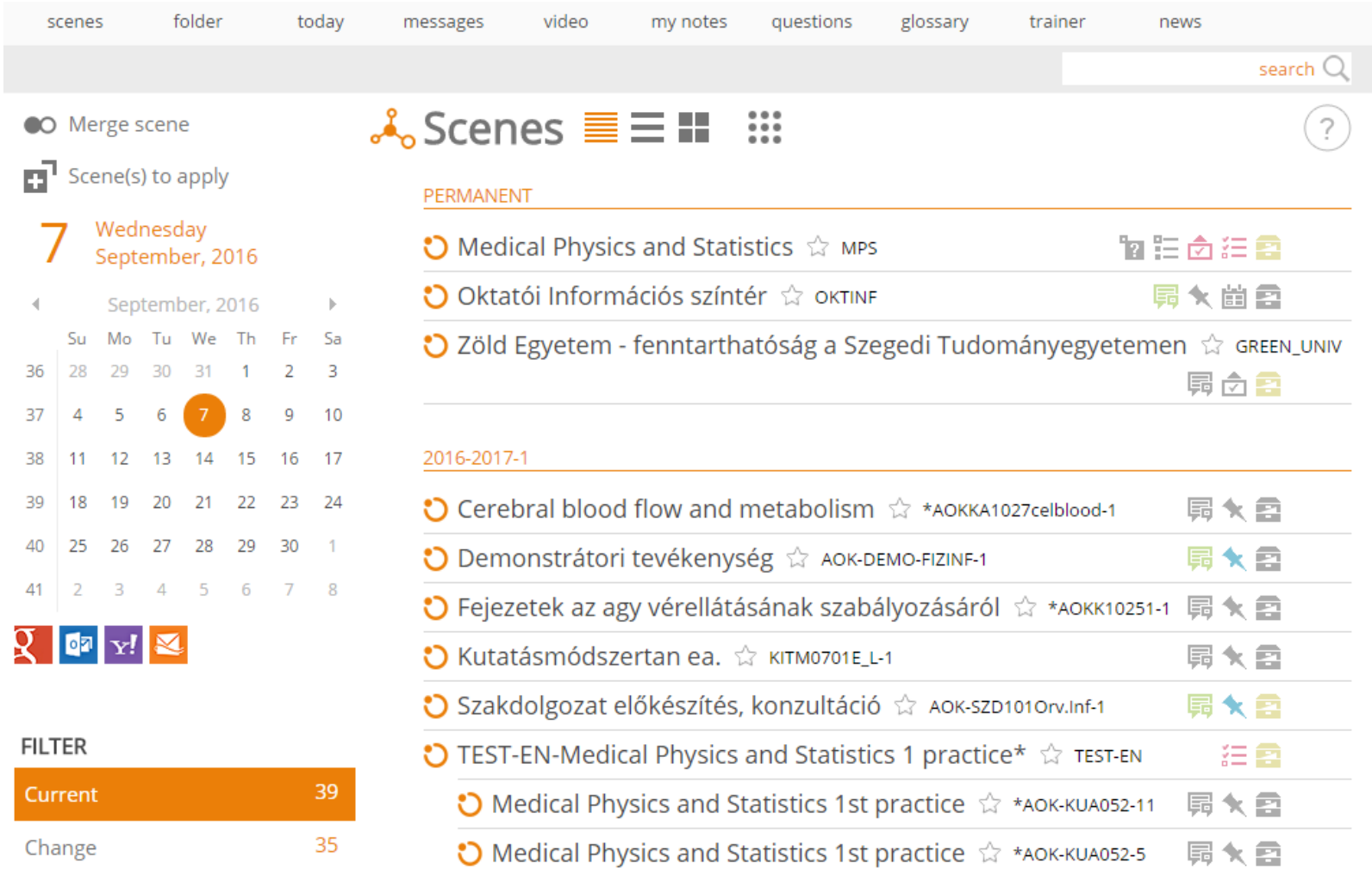

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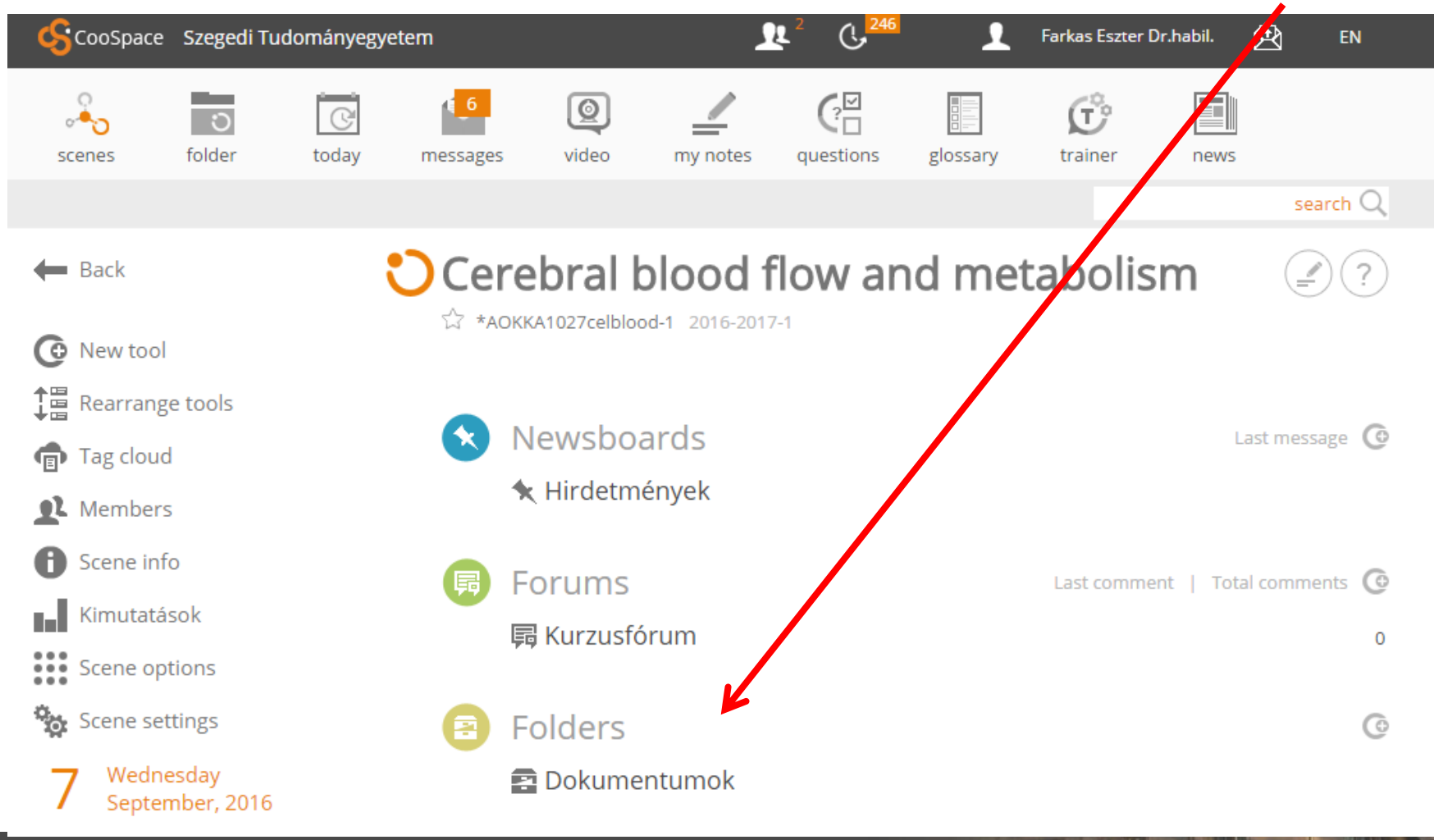
Additional study material (e.g. journal articles)



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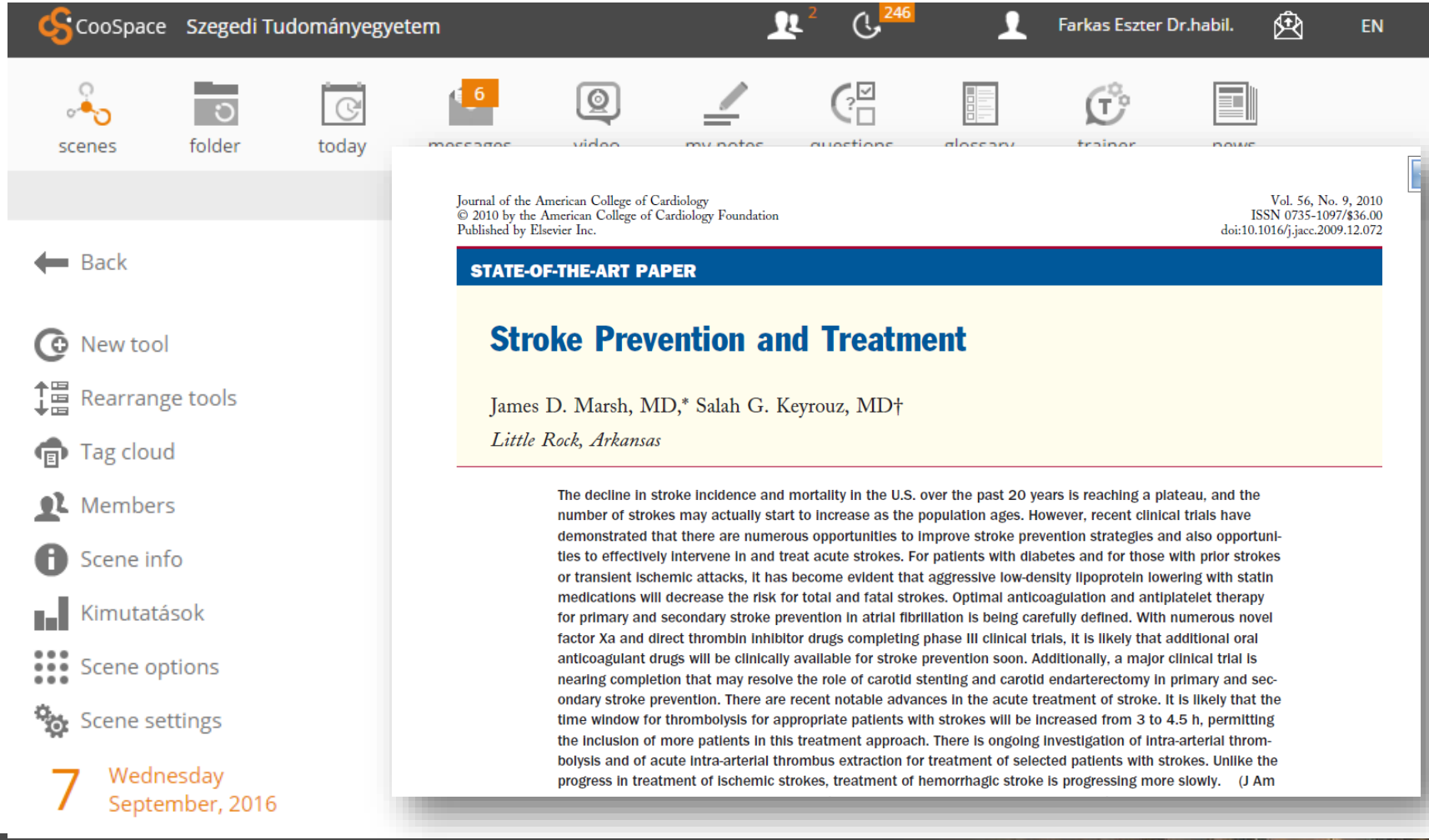
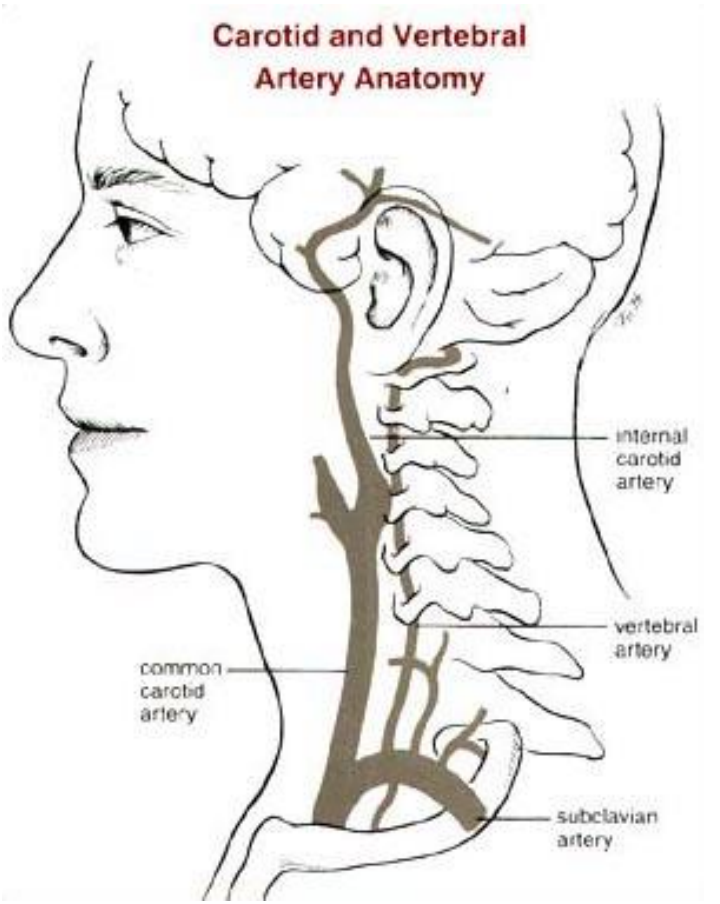
Please, read them!

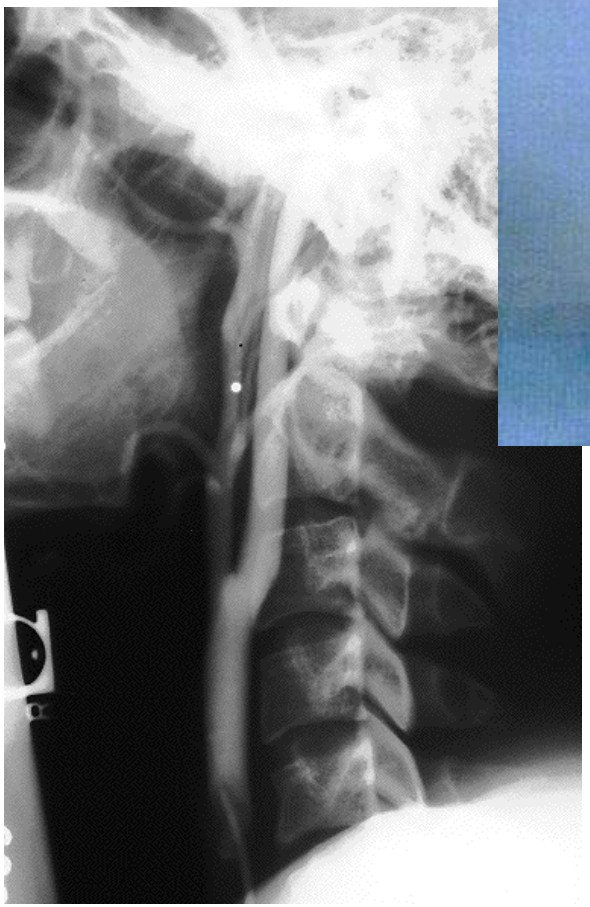


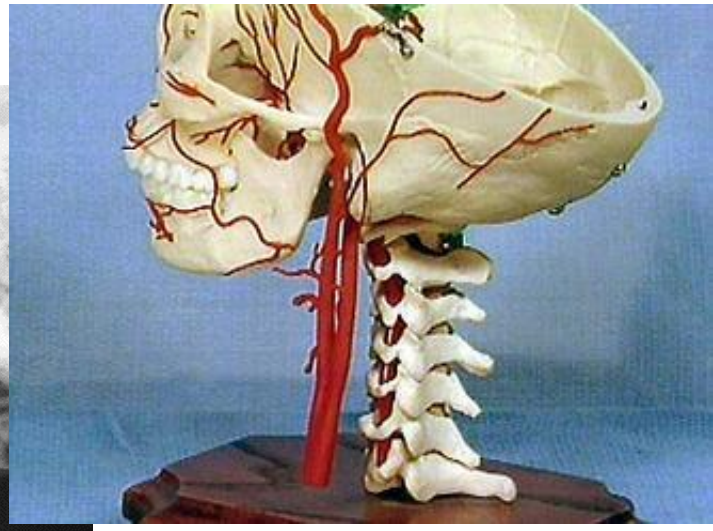
Requirements and exam

- Attendance will be checked
- Teaching material: on the website and papers recommended
- Exam: MCQ, the last week of the semester

Blood supply to the brain: extracranial vessels







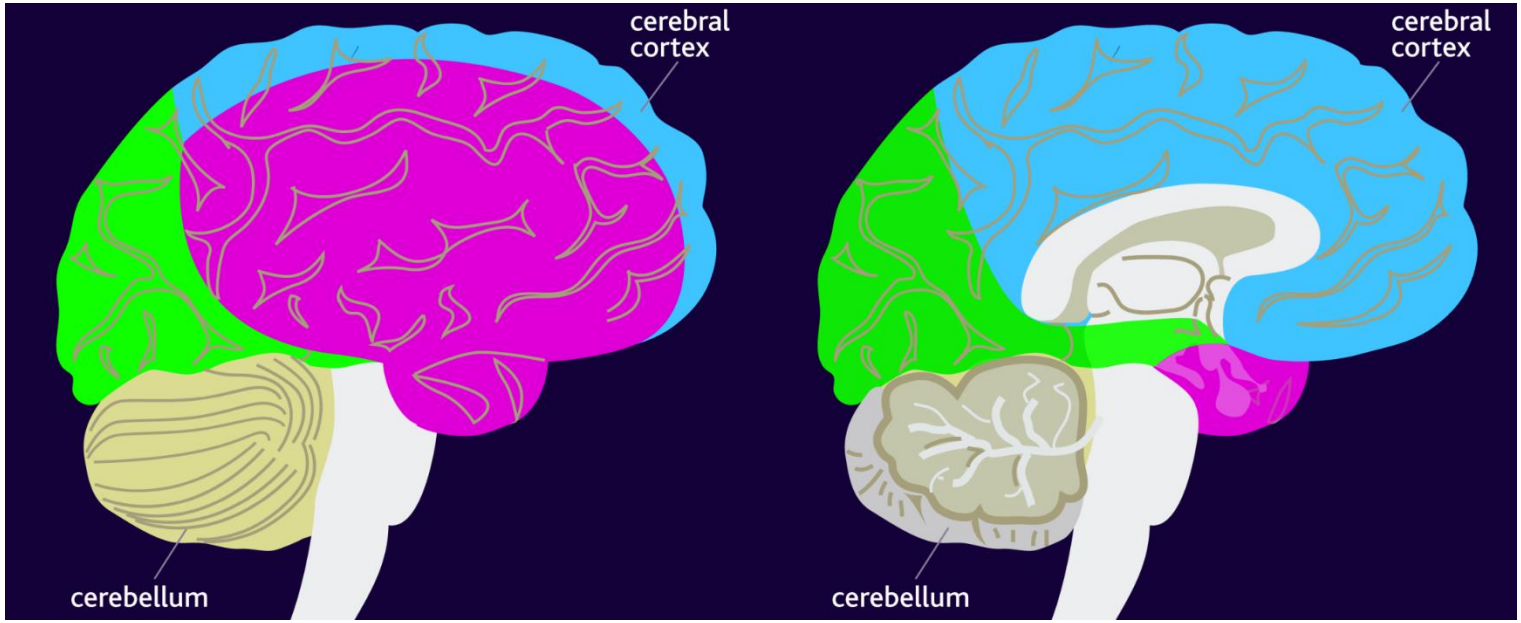
- common carotid → internal carotid
- vertebral → basilar

⇒ circle of Willis

Blood supply to the brain: Circle of Willis

Circle of communicating arteries at the base of the brain

Blood supply to the brain: intracranial vessels



Basilar A.

- ant-inf. Cerebellar A.
- int. Auditory A.
- Pontine Aa.
- sup. Cerebellar A.

POSTERIOR CEREBRAL A.

Carotidian system ~ ICA

- Hypophyseal A.
- Ophthalmic A.
- post. Communicating

MIDDLE CEREBRAL A.

ANTERIOR CEREBRAL A.

Microvessels

Blood vessels are responsible for 25-30% of total brain volume

400 miles of microvessels (with 20 m^2 surface area) provide adequate cerebral perfusion at all times

Microvessels

A lot more to come:
Blood-brain barrier lecture

Physiology: some interesting facts

Brain weight: ~2% of body weight (1400-1500g)

The brain:

- Receives 15% of the cardiac output (700-750 ml)
- Consumes 20% of the oxygen used by the entire body

Has no metabolic reserve:

- 10 seconds of interruption of blood flow to the brain leads to uncoinciousness
- 2-10 minutes interruption of blood flow may cause brain death

Physiology: some interesting facts

Continuous oxygen requirement: Neurons are predominantly aerobic

Few minutes of ischemia causes irreversible injury

- Oxygen extraction = 35%
- Oxygen supply is 3 times bigger than demand

Sensitive areas

Adults:

- Hippocampus,
- 3,5th & 6th layer of cortex,
- Purkinje cells
- Border zone (watershed areas)

Infants:

- Brain stem nuclei in infants.

Typical features of cerebral circulation

- The Monroe-Kelly hypothesis
- Autoregulation
- No sympathetic tone of blood vessels
- Blood-brain barrier
- The origin of interstitial fluid

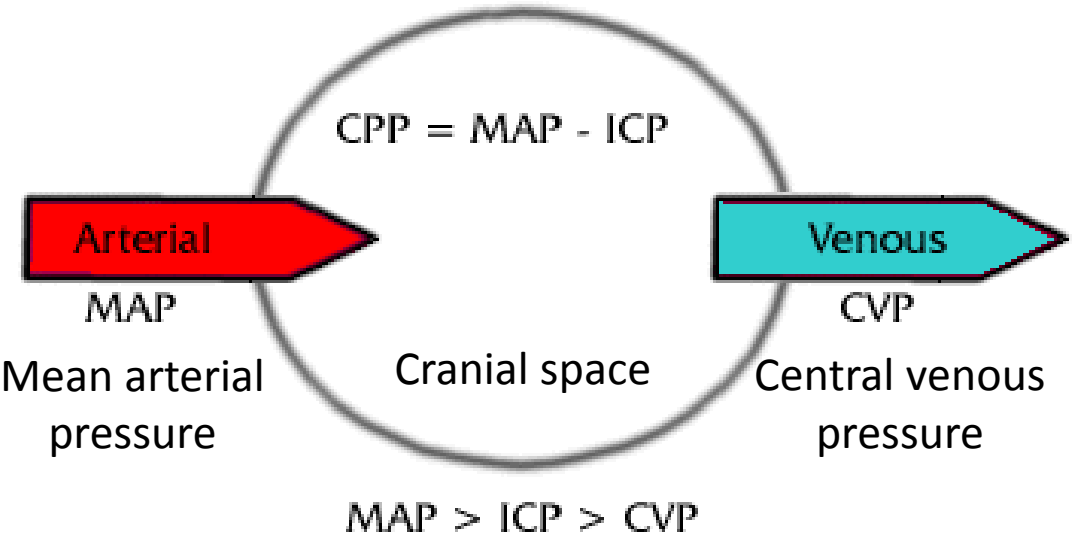
The Monroe-Kelly hypothesis

Describes the pressure relationship between cranial compartments

- Closed cranium: fixed volume - incompressible
- Compartments:
  - Brain parenchyma: 88%
  - Cerebrospinal fluid (CSF): 7-8%
  - Blood: 4-5%
- State of volume equilibrium: any increase in volume of one of the cranial constituents must be compensated by a decrease in volume of another
- Maintanence of normal intracranial pressure (ICP) at any change in volume less than approximately 100–120 ml (buffers: CSF, venous blood)
- Pathophysiologic increase in any one of the components: at the expense of the other two, increased ICP

Cerebral perfusion pressure (CPP)

- Responsible for blood supply to the brain
- Cerebral perfusion pressure (CPP) = mean arterial pressure (MAP) – intracranial pressure (ICP)
- Normal value: 70-80 mmHg
- < 50 mmHg: insufficient blood supply (ischemia)



Cerebral blood flow

- Definition: the blood supply to the brain in a given time (ml/min, v. ml/min/100g)

- Adult:
  - 750 ml/min (15% of resting cardiac output)
  - 50 ml/min/100g

- Defining variables: $$CBF = \frac{CPP}{CVR} \qquad CPP = MAP\text{-}ICP$$

  (CVR: cerebrovascular resistance)

Cerebral blood flow regulation

Cathegories:

Affected area:

- Global
- Local

Type:

- Myogenic
- Neurogenic
- Metabolic
  Chemical

Origin of stimulus:

- Parenchyma
- Endothelium
- Blood

Cerebral blood flow regulation

A lot more to come!

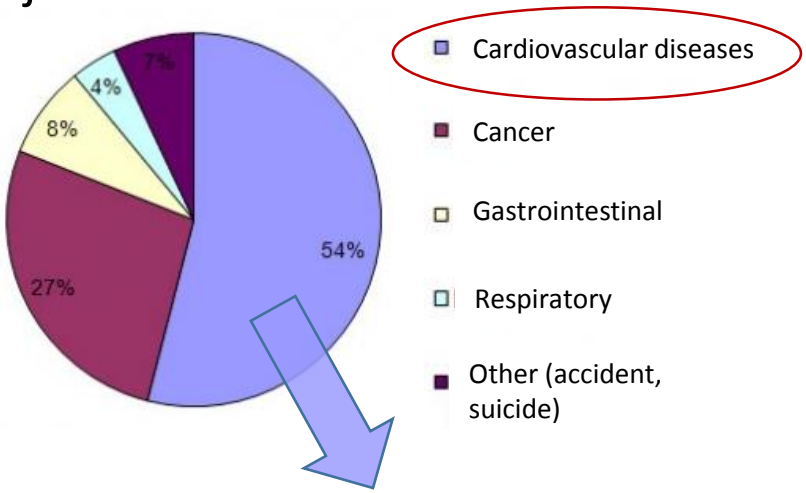
Cerebrovascular diseases

- Common denominator: ischemia
- What is ischemia?

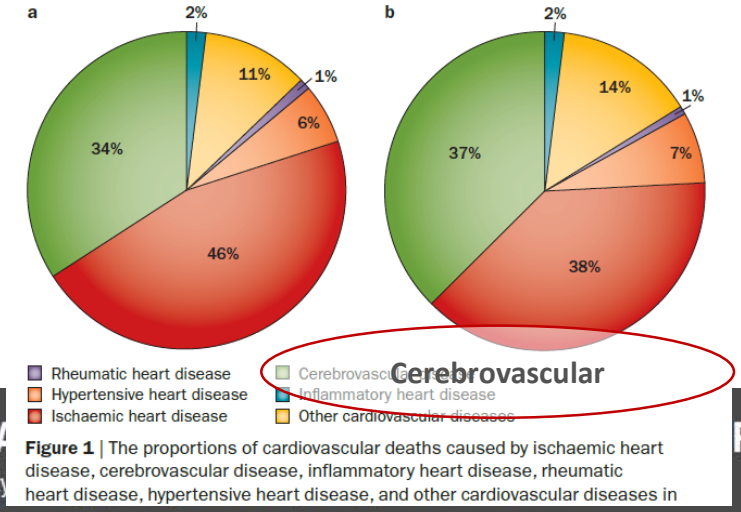
An inadequate blood supply to an organ or part of the body ⇨ shortage of oxygen and glucose needed for cellular metabolism

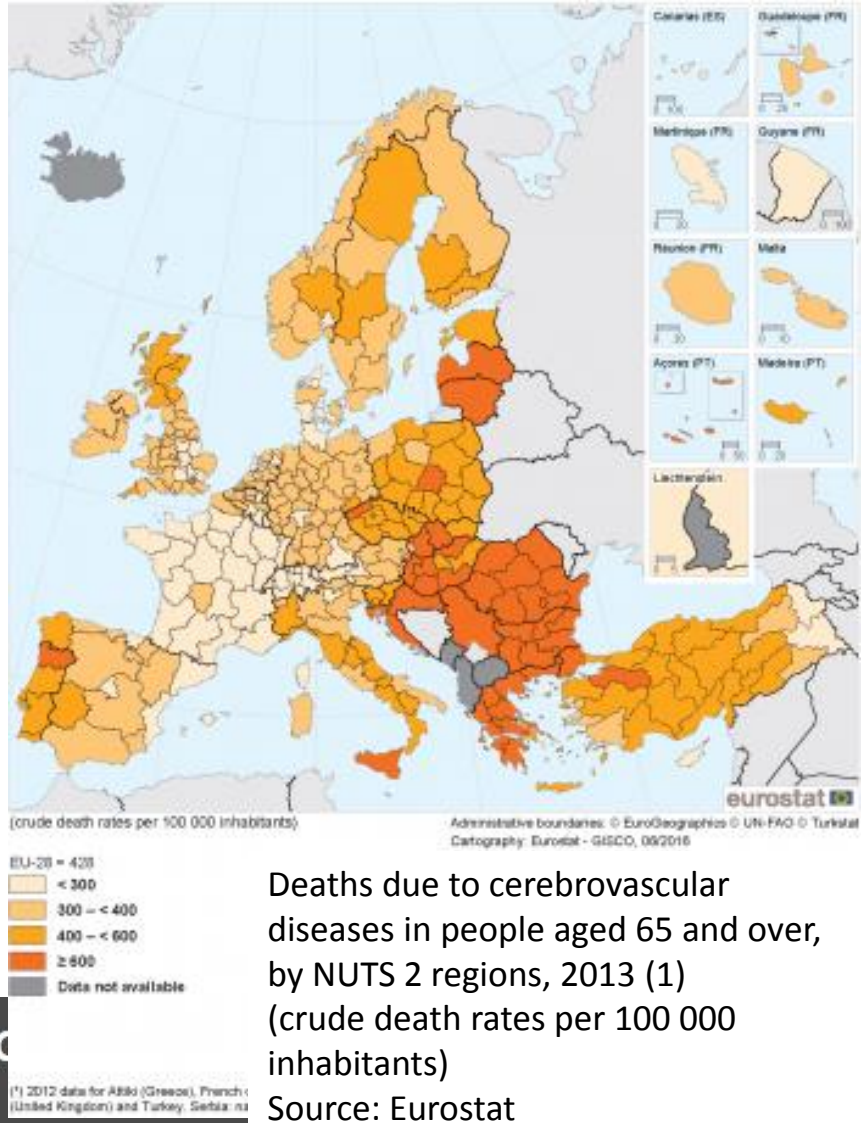
Cerebrovascular diseases

Major causes of death



Cardiovascular diseases:





Deaths due to cerebrovascular diseases in people aged 65 and over, by NUTS 2 regions, 2013 (1) (crude death rates per 100 000 inhabitants)
Source: Eurostat

White matter lesions
Alzheimer's disease
Vascular Cognitive Impairment
Stroke

Clinical Categories of Inadequacy

1. Global Ischemia

   Hypotension, hypoxemia, anemia

   ↓

   Hypoxemic encephalopathy

2. Focal Ischemia

   Obstruction to blood supply to focal area

   Thrombosis, embolism or hemorrhage

Global ischemia

Etiology:

- Impaired blood supply - Lung & Heart disorders
- Impaired O_2 carrying – Anemia/Blood disorders

Morphology:

- Laminar necrosis, damage in: Hippocampus, Purkinje cells
- Border zone infarcts – “Watershed”
- Sickle shaped band of necrosis on cortex.

Clinical Features:

Mild transient confusion state

Severe irreversible brain death; flat EEG, vegetative state, coma

Global ischemia

Mild cognitive impairment

Dementia

- Alzheimer's Disease, cerebral amyloid angiopathy
- CADASIL (Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy): mutations of the Notch 3 gene on chromosome 19
- Cerebral microhemorrhage - results from rupture of small blood vessels
- Multi-infarct dementia - multiple strokes (disruption of blood flow to the brain)

Alzheimer's disease

An upcoming lecture dedicated to the topic!

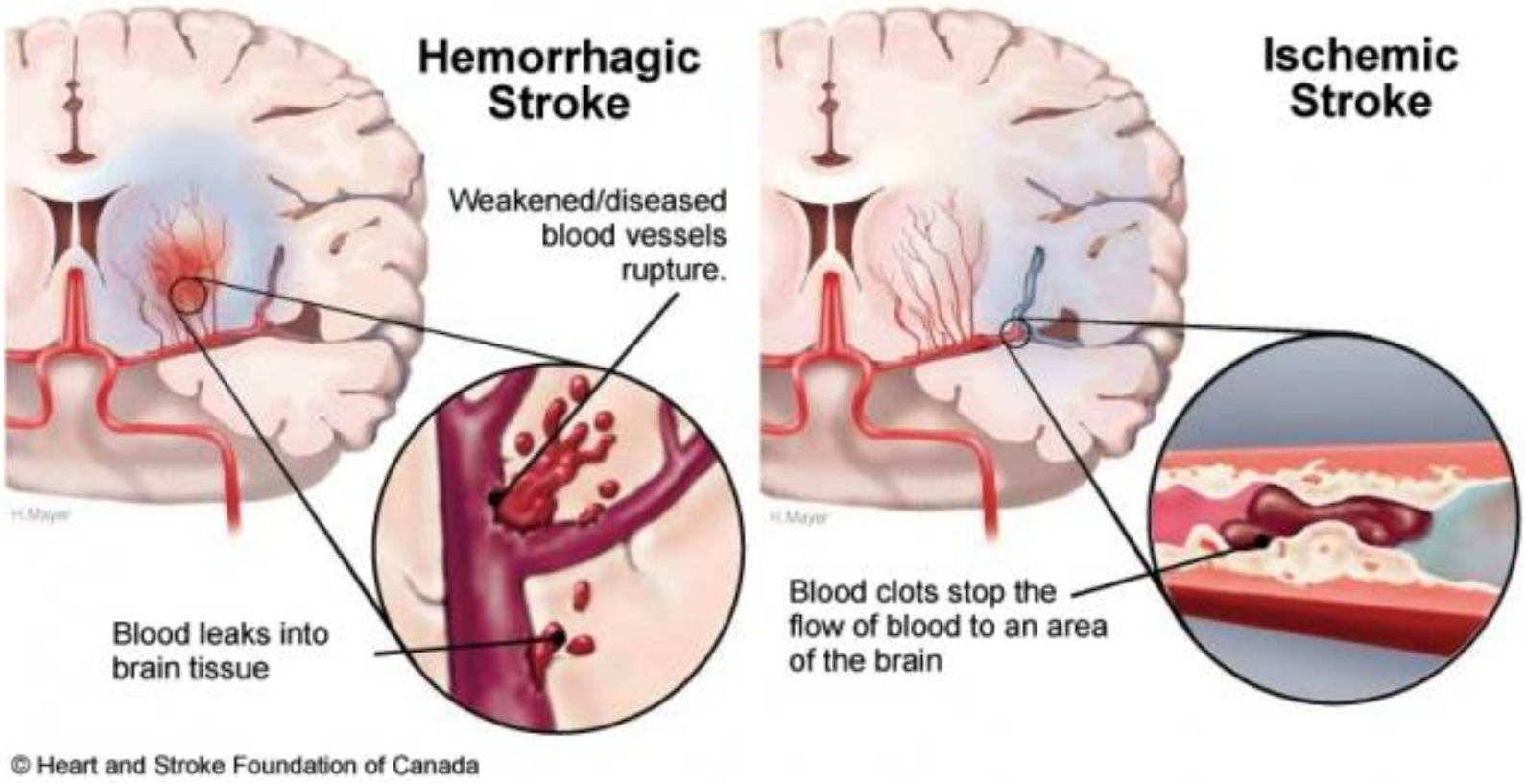
Focal ischemia

Cessation of blood circulation, oxygen and nutrients in a particular region of brain

~ Stroke

Definition of stroke

Cerebro-vascular disorder caused by insufficient cerebral circulation, and resulting in sudden neurological deficits.



Incidence

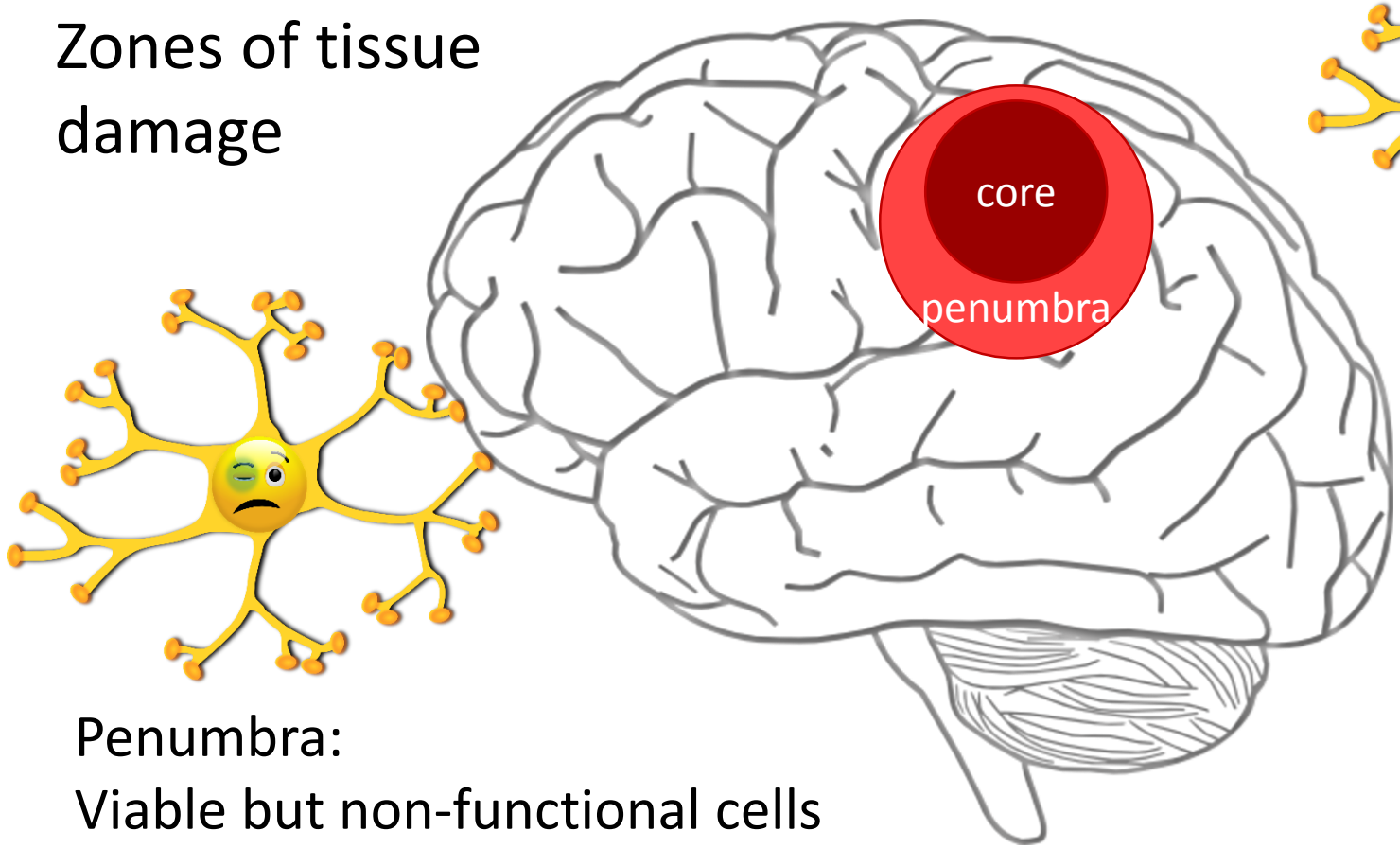
- Hemorrhage: bleeding, within the skull

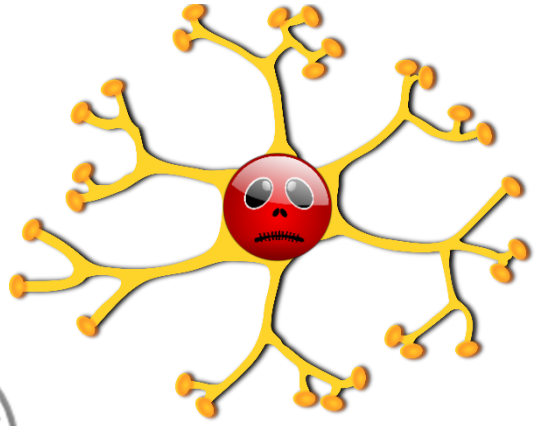
  Incidence 20% - mortality 80%
  - Intracerebral or subarachnoid
  - Aneurysm (hypertension/congenital), arteriovenous malformation
- Infarction: tissue death (necrosis) due to a local lack of oxygen caused by obstruction of the tissue's blood supply.

  Incidence 80% - mortality 40%
  - 50% - Thrombotic – atherosclerosis
    - Large-vessel 30% (carotid, middle cerebral)
    - Small vessel 20% (lacunar stroke)
  - 30% Embolic (heart disease/atherosclerosis)
    - Young, rapid, extensive

Infarction (ischemic stroke)

Zones of tissue damage





Core (umbra):
Infarcted area – non-viable cells

Penumbra:
Viable but non-functional cells

Residual blood flow

Collateral circulation helps to maintain some CBF to post obstruction area

- Core ~ CBF < 10 ml/100gm/min

  Early irreversible membrane rupture & cell death

- Penumbra ~ CBF < 20 ml/100gm/min

  Rapid energy depletion & loss of neuronal activity (electrically silent)

Infarct maturation

Reduced blood supply ⇨ hypoxia/anoxia

Altered metabolism ⇨ Na/K pump block

Glutamate receptor activation ⇨ Ca influx

1-6 min – ischemic injury

>6 min – cell death

Duration of ischemia ⇨ infarct maturation

- Animal models & human studies (MRI, PET) of acute ischemia shows:

< 2 hrs	reversible neuronal deficit
> 6 hrs	irreversible neuronal deficit

Clinical studies & current therapies aim for reperfusion within 2 to 6 hrs *(therapeutic window)*

Stages of infarct maturation

- Immediate – 6 hours; no change (both macro & micro)
- Acute stage – 2 days; edema, loss of grey/white matter border, inflammation, red neurons, neutrophils
- Intermediate stage – 2 weeks; demarcation, soft friable tissue, cysts; macrophages, liquifactive necrosis
- Late) stage – after 4 weeks; fluid filled cysts with dark grey margin (gliosis), removal of tissue by macrophages
- Gliosis – proliferation of glia, loss of architecture

Stroke

An upcoming lecture dedicated to the topic!