

MUNI I

MED

# **Pathophysiology of Central Nervous System**

**Stroke**

**Brain injury**

Spinal cord injury

# Intracranial Compartments, Intracranial Pressure and Cerebral Perfusion Pressure

Brain is enclosed in the skull...

... an advantage before trouble occurs...

... big problem after trouble occurs.

## Intracranial compartments

- Brain
- Cerebrospinal fluid (CSF)
- Blood

## Intracranial pressure (ICP)

- Pressure inside the skull

## Cerebral perfusion pressure

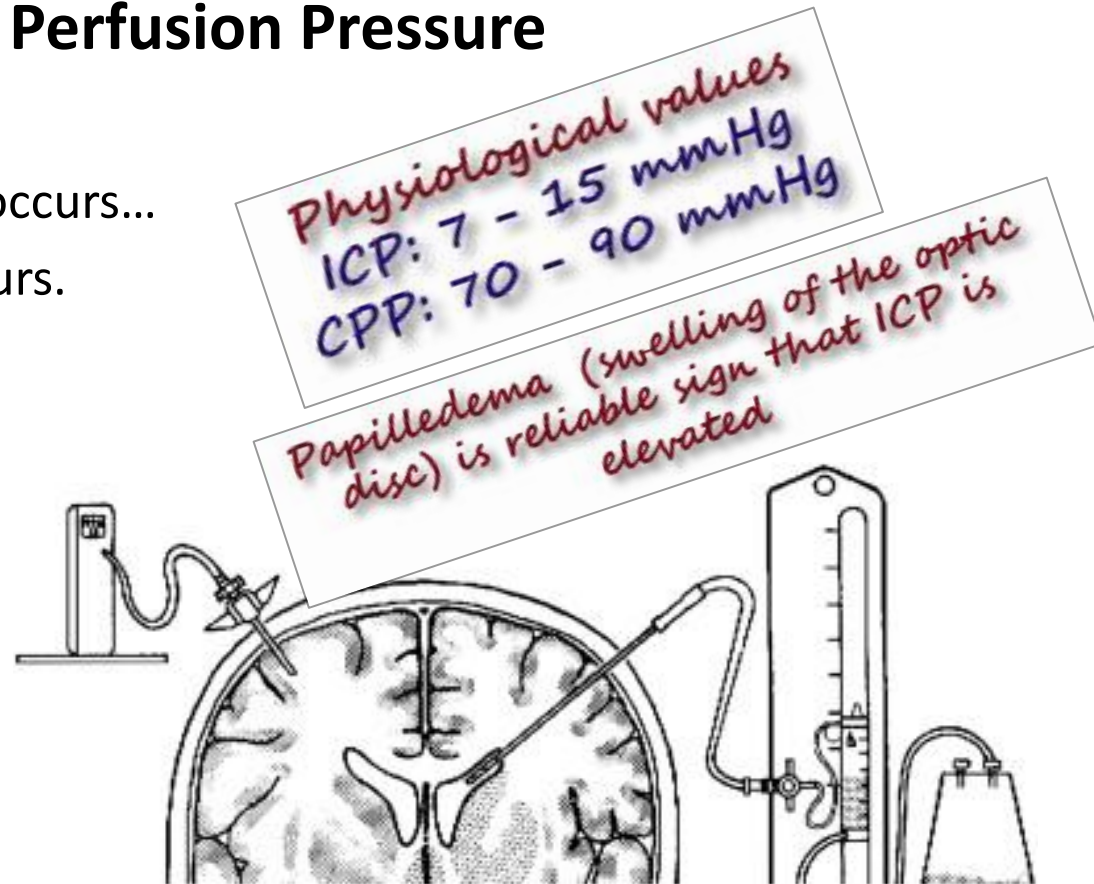
- The pressure gradient through which blood flows to the brain

$$\text{CPP} = \text{MAP} - \text{ICP}$$

Cerebral perfusion pressure

Intracranial pressure

Mean arterial pressure



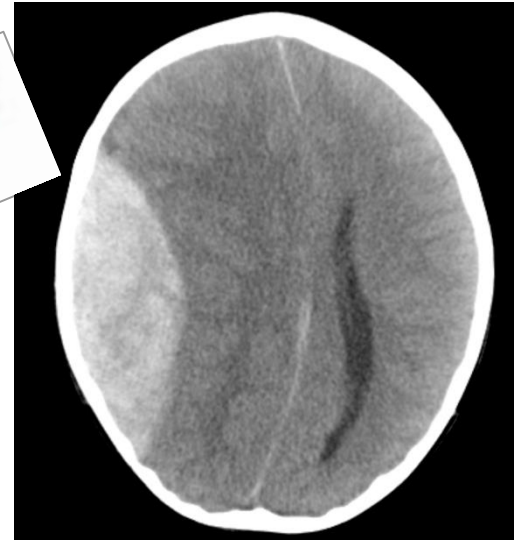
<http://ars.els-cdn.com>

# Causes of Intracranial Hypertension

## Brain compartment

- Edema
- Tumor
- Hemorrhage
- Infection

*Dynamic of development is an important factor.*



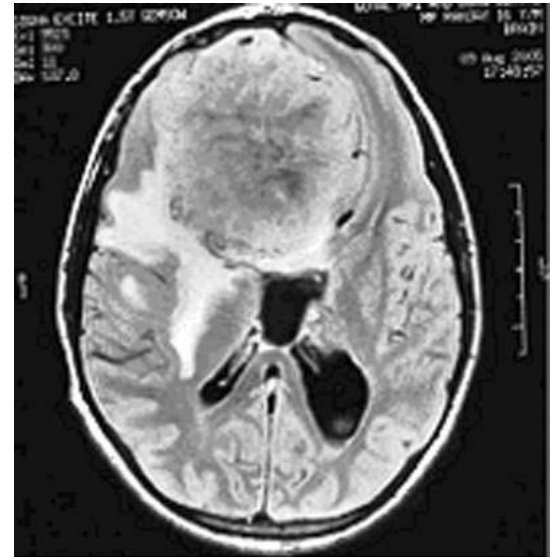
## CSF compartment

- Hydrocephalus

## Compartment of blood

- Venous sinus thrombosis
- Acidosis - ischemia

*Lumbar puncture should not be performed if there is intracranial hypertension. Cerebral herniation may occur in such a case.*



# Causes of Intracranial Hypertension

## Brain Edema

### Cytotoxic (intracellular)

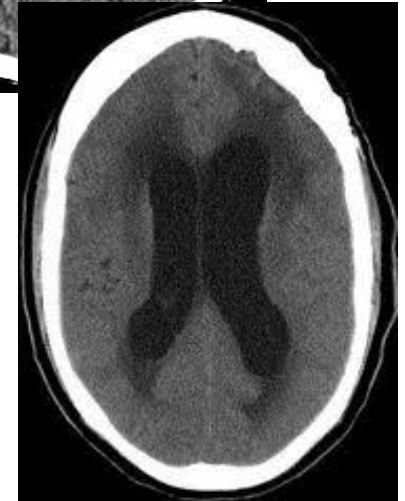
- Na/K ATPase failure
- Na or Ca influx
- H<sub>2</sub>O
- Mainly occurs in first 24 h. following insult

### Vazogenic (extracellular)

- Damage of endothelial cells and Blood – Brain barrier
- Extravasation of proteins and electrolytes into Interstitial space
- Mainly occurs at 24 h. after insult and later
- Neovascularization of tumor – imperfect vessels

### Interstitial

- Obstruction of CSF circulation
- Mechanical damage of CSF- brain barrier
- Infiltration of CSF into interstitial space



# Causes of Intracranial Hypertension

## Hydrocephalus

**Abnormal accumulation of CSF in liquor space**

### CSF production

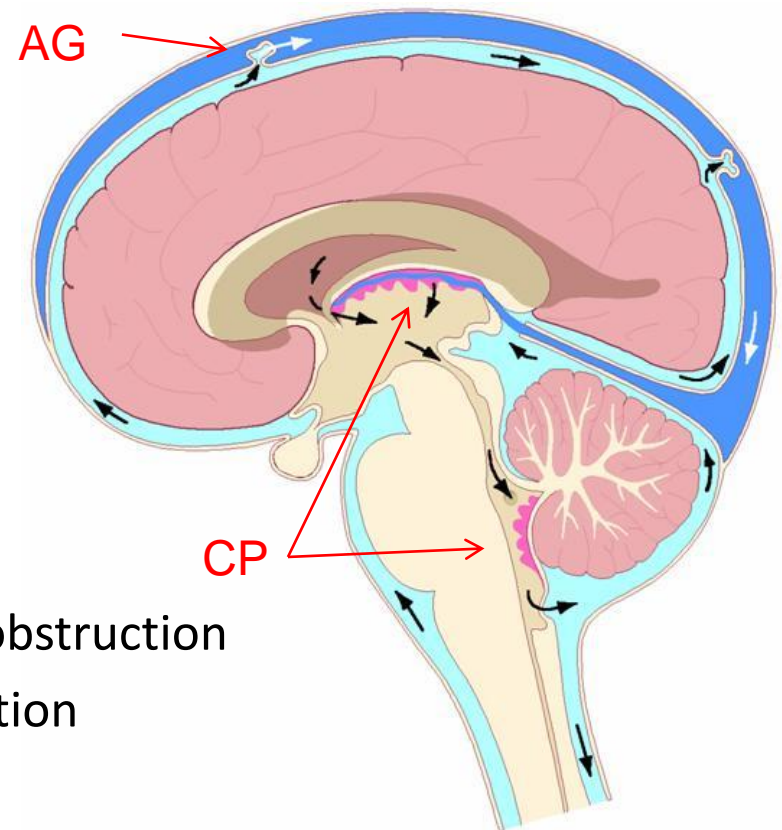
- Choroid plexus (CP)
- 450-750 ml/day

### CSF resorption

- Archnoid granulations (AG)

### Hydrocephalus

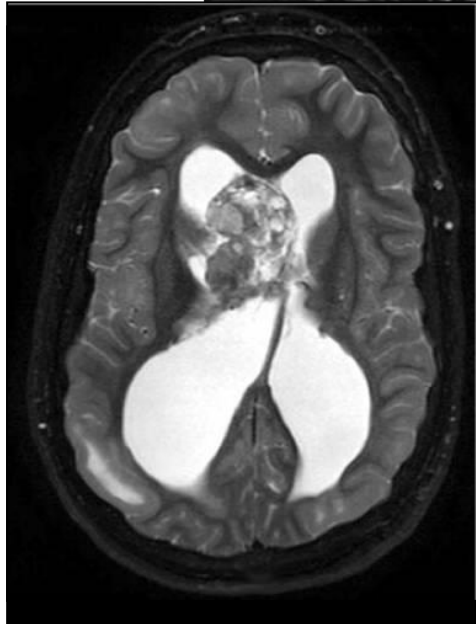
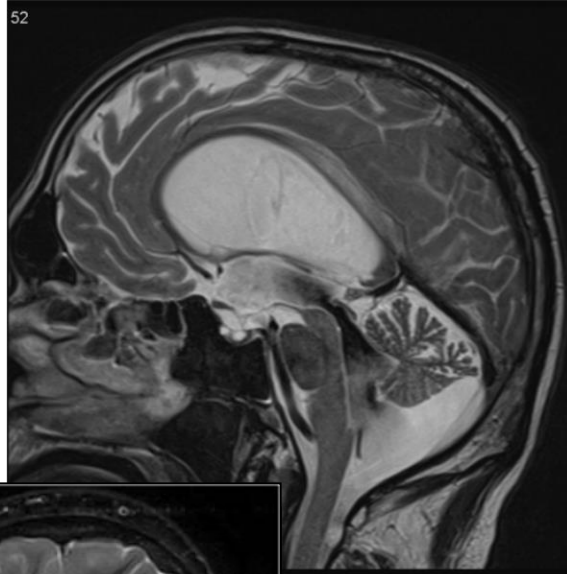
- Obstructive (Non- communicating)
  - ✓ Impaired CSF circulation due to obstruction
  - ✓ For example: ventricular obstruction
- Non – obstructive (Communicating)
  - ✓ Impaired CSF resorption



**Acute X Chronic**

# Causes of Intracranial Hypertension

## Hydrocephalus





# Consequences of Intracranial Hypertension

## Compression of adjacent tissue

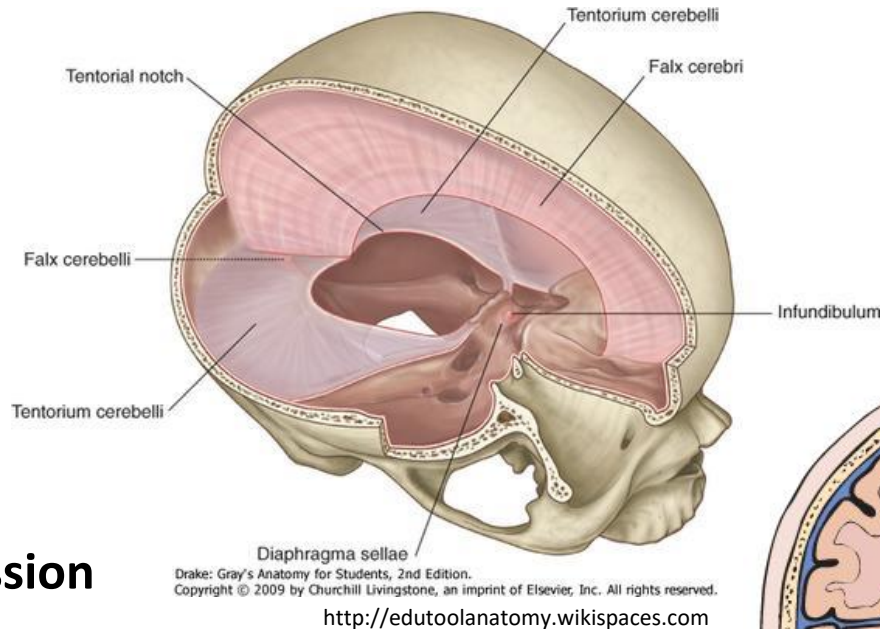
- Ischemization

## Infratentorial lesions

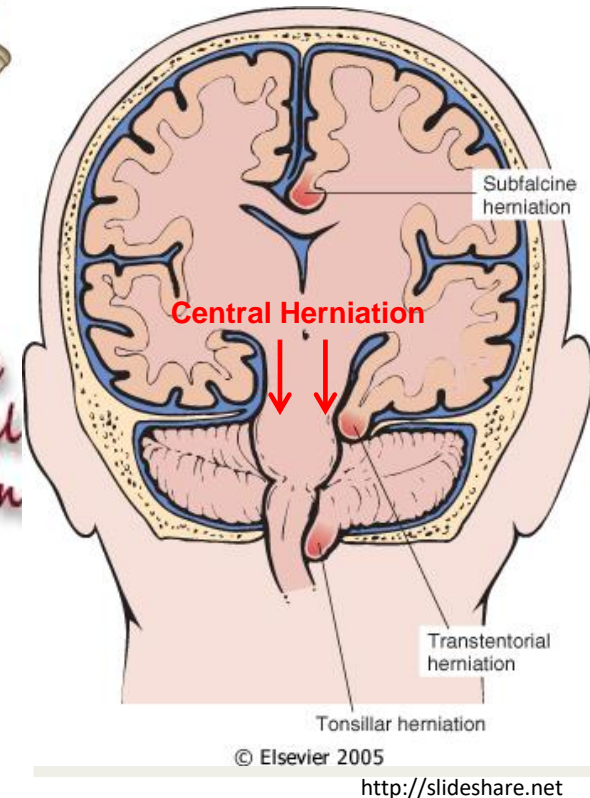
- Always acute
- Risk of brain stem compression
- stem compression

## Cerebral herniation

- Subfalcine
- Transtentorial
- Tonsillar
- Central
- ✓ Permanent damage of brain
- ✓ Risk of brain stem compression



*Lumbar puncture should not be performed if there is intracranial hypertension. Cerebral herniation may occur in such a case.*



**Stroke**

Cerebrovascular disease by country (per 100,000 inhabitants).



<http://wikipedia.org>

**Stroke**  
Third leading cause of death worldwide  
Nearly 50 millions new cases each year  
worldwide  
Rate of mortality nearly 25%

# Stroke

**Stroke is an acute neurological dysfunction due to vascular disturbance resulting in rapid loss of brain functions**

## Vascular pathologies

- Disturbance of vessel wall permeability
- Disturbance of vessel contractility
- Vessel occlusion
  - ✓ Thrombosis
  - ✓ Embolism
- Vessel rupture

## Atherosclerosis

### Types of stroke

- Ischemic (70%)
- Hemorrhagic (30%)
  - ✓ Intracerebral hematoma
  - ✓ Subarachnoid hemorrhage



# Ischemic Stroke

## Critical parameters

- Extent of ischemia
- Duration of ischemia

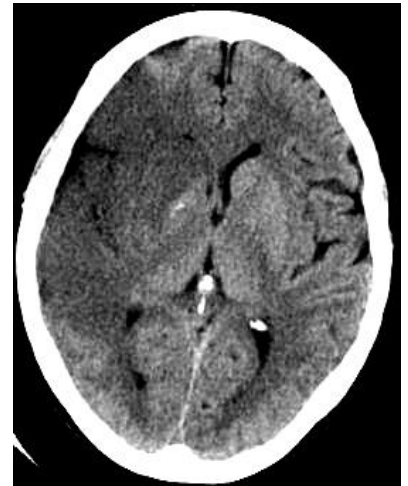
## Atherosclerosis

## Focal ischemic stroke

- **Transient**
  - ✓ Transient ischemic attack (TIA)
  - ✓ Prolonged reversible neurological deficit
- **Permanent**
  - ✓ Cerebral infarction
    - ❖ Embolism
    - ❖ Thrombosis

## Global ischemic stroke

- **Transient**
  - ✓ Syncope
- **Permanent**
  - ✓ Hypoxic ischemic encephalopathy



# Why is brain sensitive to ischemia?



<http://assassinscreed.ubi.com>

*Tissue resistance to ischemia*  
Brain: less than 5 min.  
Liver and kidney: 15 - 20 min.  
Skeletal muscle: 60 - 90 min.  
Visceral muscle: 24 - 72 hours  
Hair: several days

## High metabolic activity

- Membrane potential maintaining – repolarisation (Na/K pumps)
- Almost exclusively oxidative phosphorylation
- Consumption
  - ✓ Oxygen- 20% of body consumption
  - ✓ Glucose – 25% of body consumption

## Small amount of energy reserves

# Ischemic Stroke

## Core of infarction (centre of ischemia)

- Irreversible neuronal damage
- Primary injury

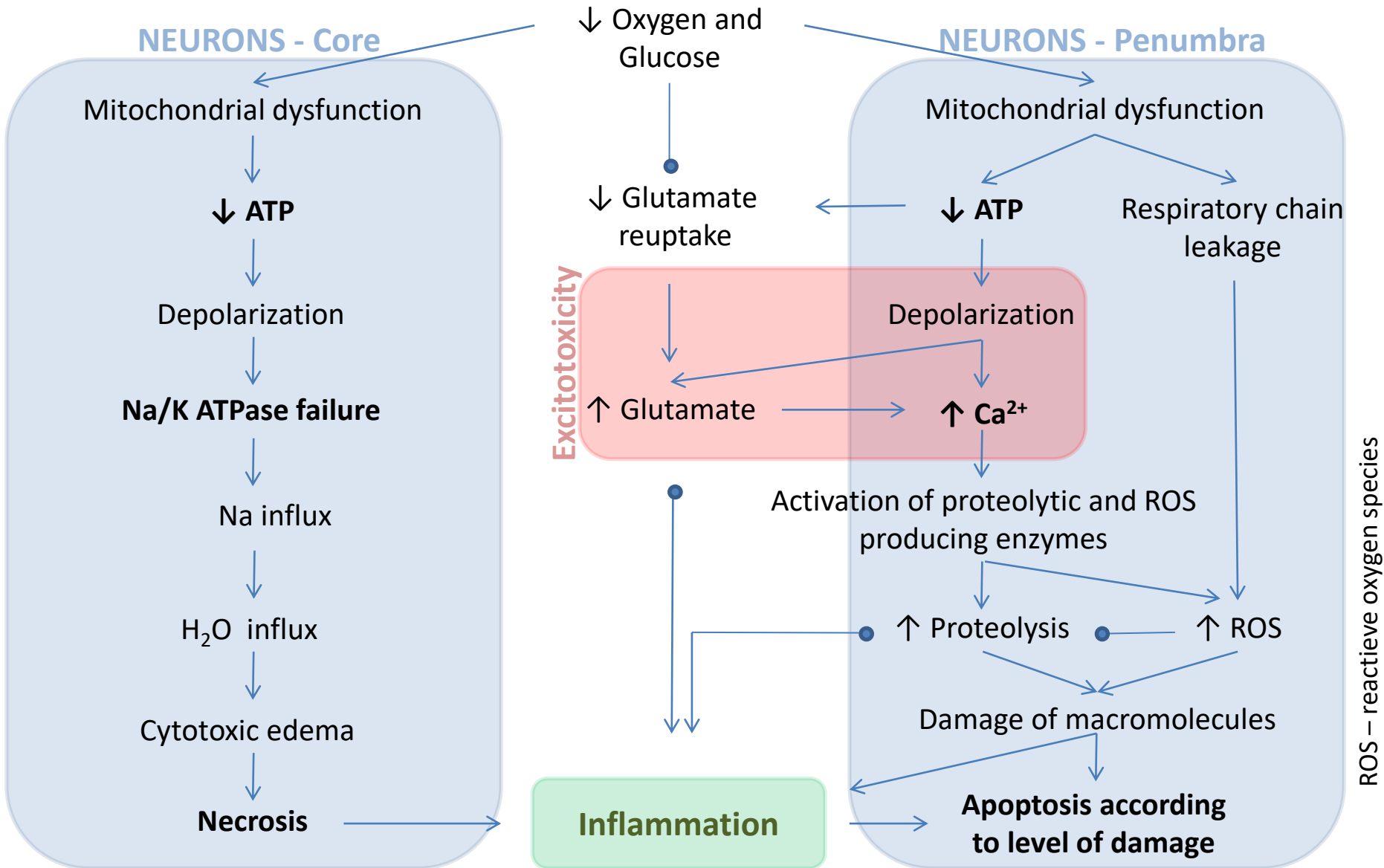
## Penumbra (periphery of ischemia)

- Reversible neuronal damage
- Risk of secondary injury development

**Primary brain injury**  
Directly caused by the pathology  
Developed in the same time  
as pathology occurs  
Non treatable

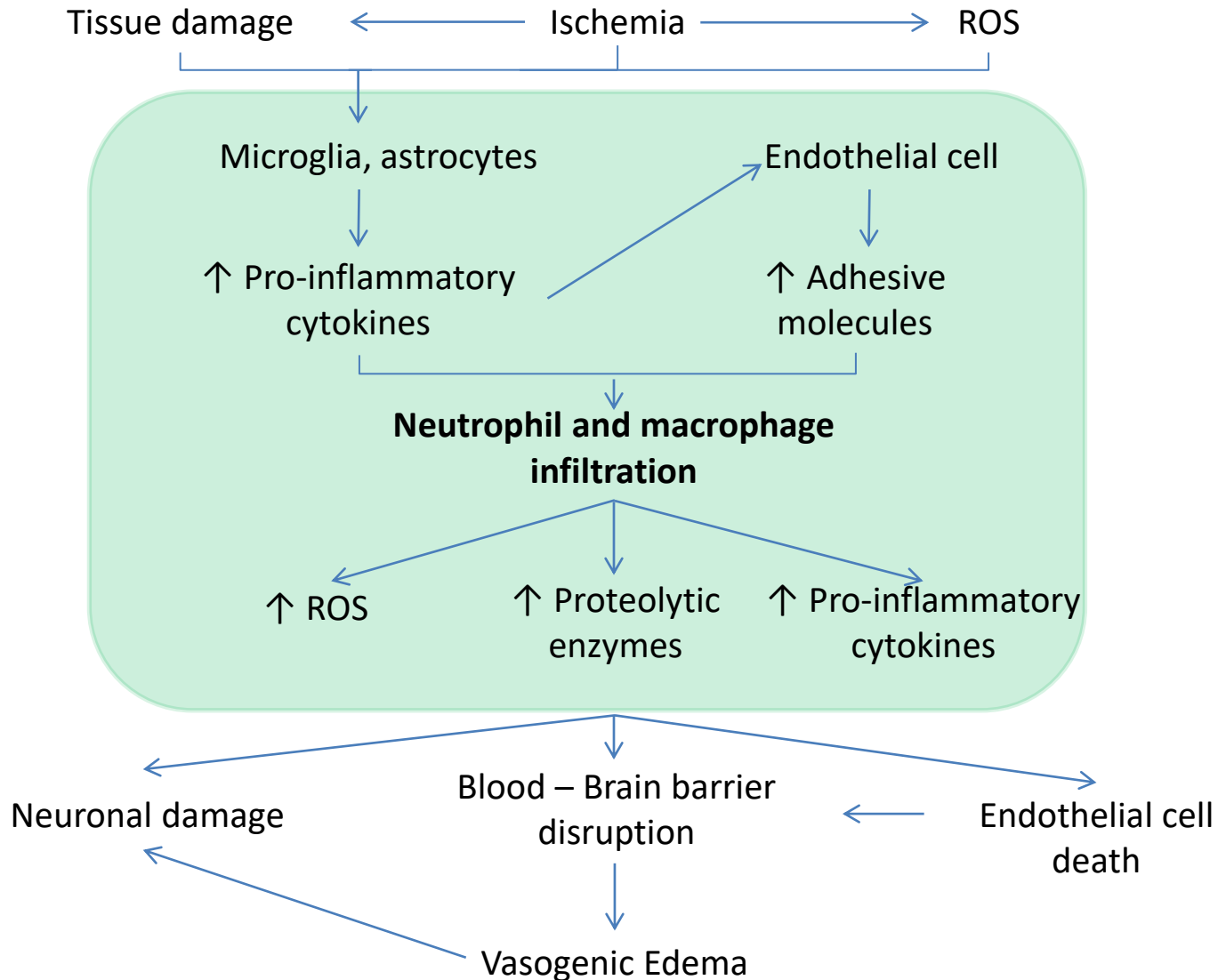
**Secondary brain injury**  
Caused by reaction of organism  
to pathology  
Developed in delayed manner  
Potentially treatable

# Ischemic Cascade





# Role of Inflammation in Ischemic Cascade



# Mechanisms of Ischemic Damage

## Excitotoxicity

### Accumulation of excitatory neurotransmitters in extracellular space

- Glutamate
- Aspartate

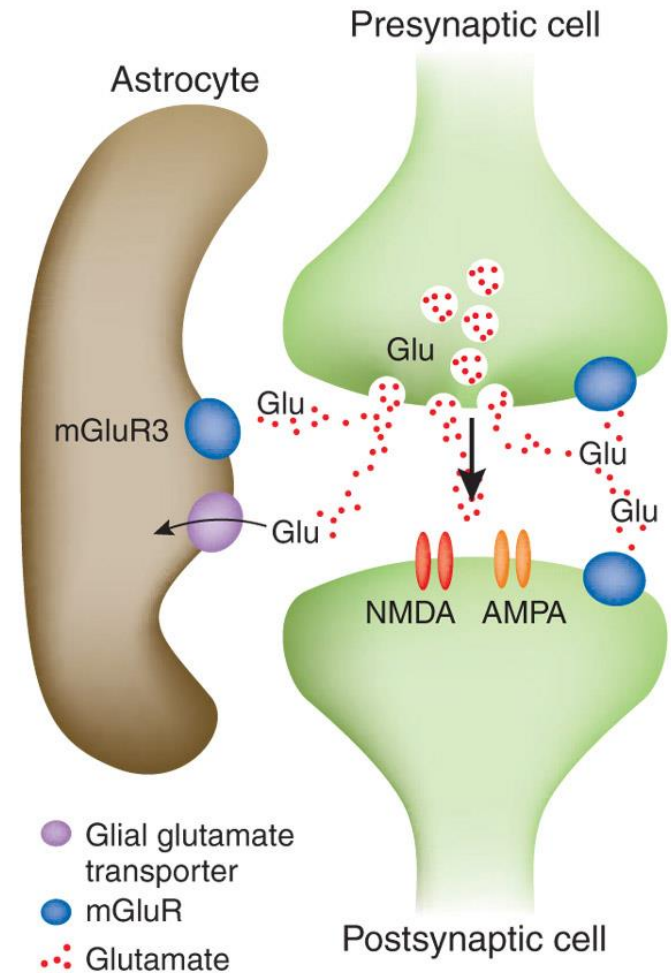
### Neuronal damage due to excessive stimulation

#### Cause

- Depolarization
- Decreased reuptake

#### Consequence

- Stimulation of adjacent neurons
- Ca overload
  - Proteolysis
  - Excessive ROS production
  - Cytotoxic edema



# Mechanisms of Ischemic Damage

## Reactive oxygen species (ROS)

ROS are highly reactive particles

ROS are mainly produced during reperfusion

### Cause

- Intracellular
  - ✓ Respiratory chain leakage
    - ❖ Disruption of electron transport chains in mitochondria
  - ✓ Ca – overload – activation of ROS producing enzymes
- Extracellular
  - ✓ Inflammation

### Consequence

- Lipid peroxidation – damage of membranes
- Protein oxidation – damage of enzymes and structural proteins
- Oxidation of purin a pyrimidine bases – damage of DNA
- Stimulation of inflammatory response

**Reactive oxygen species**

Superoxide:  $O_2^{\bullet-}$

Hydroxyl radical:  $OH^\bullet$

Hydrogen peroxide:  $H_2O_2$

# Mechanisms of Ischemic Damage

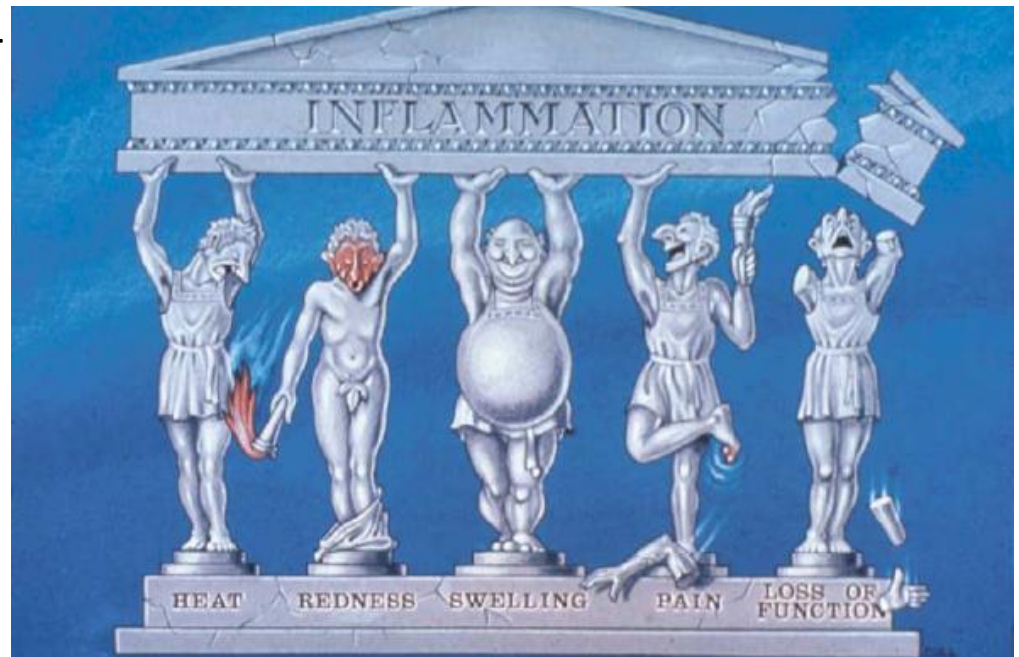
## Inflammation

### Cause

- Ischemia and tissue damage trigger production of
  - ✓ Pro – inflammatory cytokines – activation of leukocytes in periphery
  - ✓ Adhesive molecules – attraction of leukocytes to damaged area
- Infiltrating leukocytes produce
  - ✓ Proteolytic enzymes –
  - ✓ Pro – infl. Cytokines
  - ✓ ROS

### Consequence

- Damage of
  - ✓ Endothelial cells
  - ✓ Blood – Brain barrier
  - ✓ Neuronal cells



# Hemorrhagic Stroke

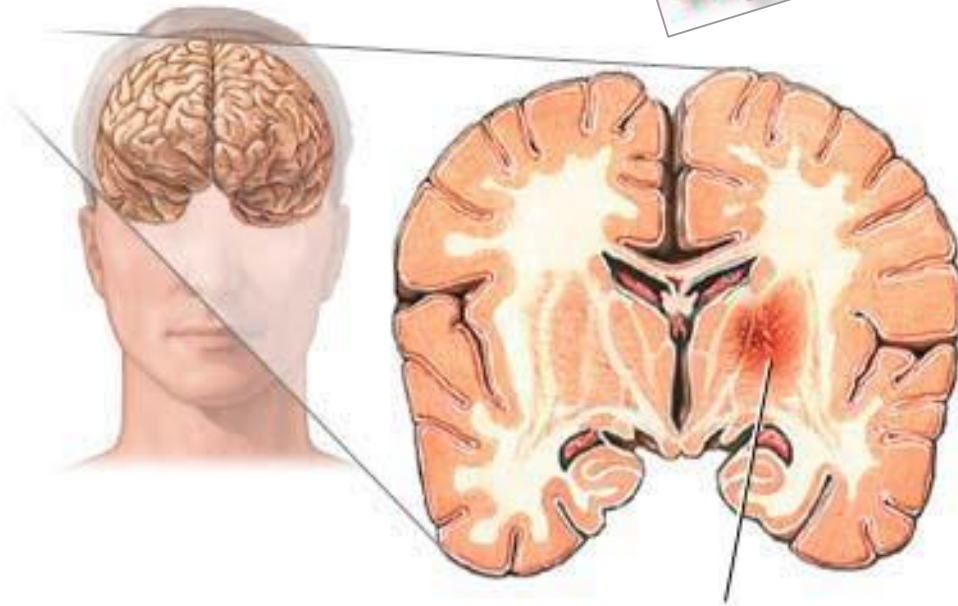
## Intracerebral hematoma (ICH)

Bleeding into the brain parenchyma (intraaxial)

The most often localization

- Basal ganglia
- Thalamus

*Arterial hypertension*



Intracerebral hemorrhage



# Pathophysiology of ICH

Hematoma

**Mass effect**

Mechanical damage of brain parenchyma

↑ ICP

Transient ischemia

Inflammation

Excitotoxicity

↑ ROS (Neurons)

↑ Proteolysis (Neurons)

**Cytotoxic blood components**

Complement Etc.

Hemoglobin

Fe<sup>2+</sup>

↑ ROS

Endothelial cell death

**Neuronal cell death**

**Inflammation**

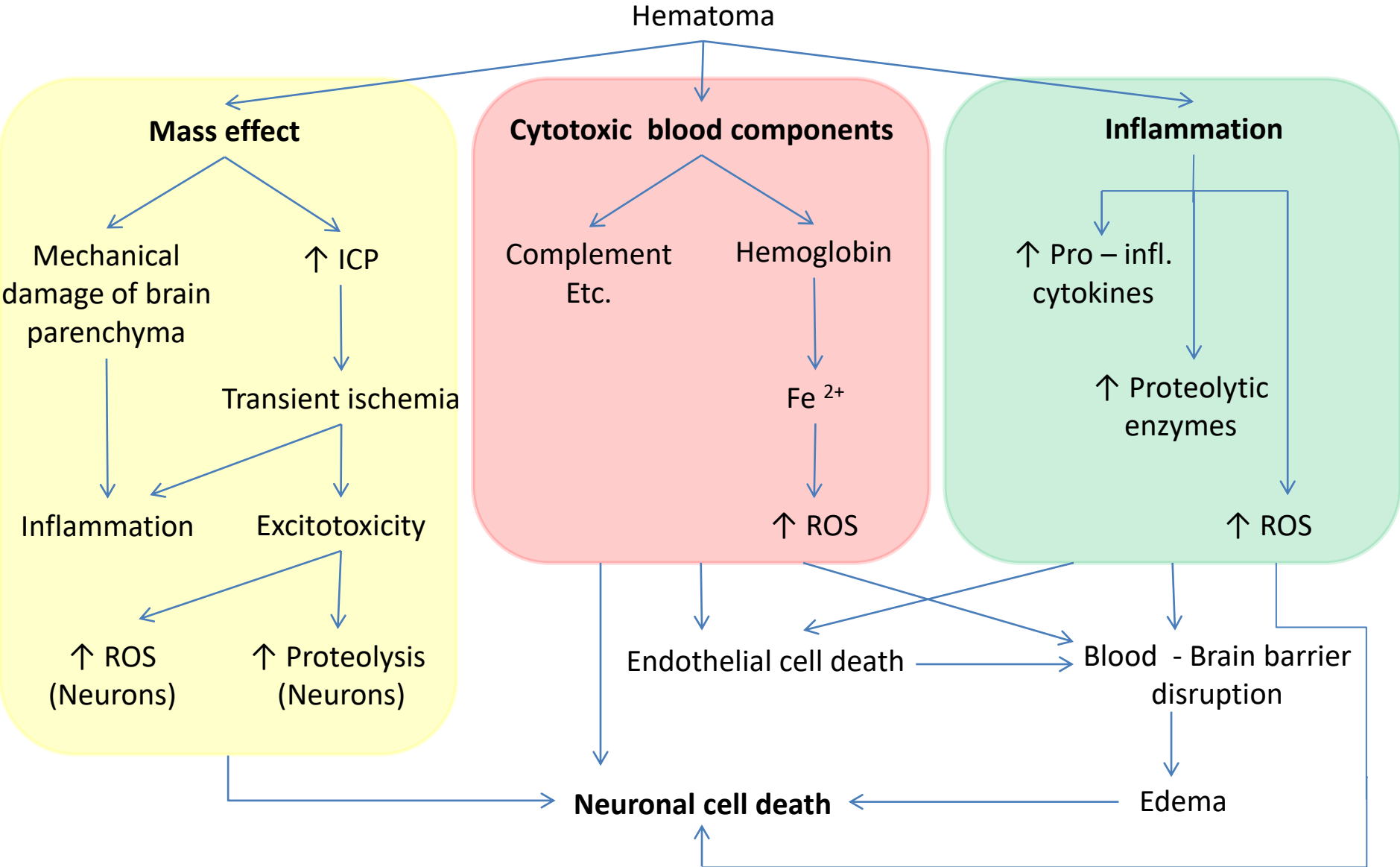
↑ Pro - infl. cytokines

↑ Proteolytic enzymes

↑ ROS

Blood - Brain barrier disruption

Edema

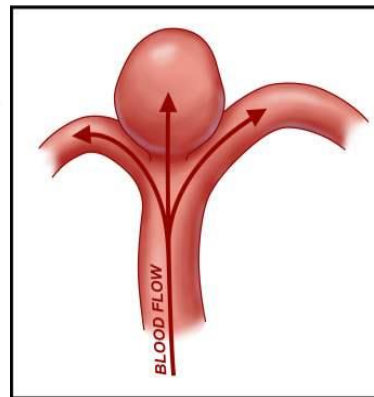
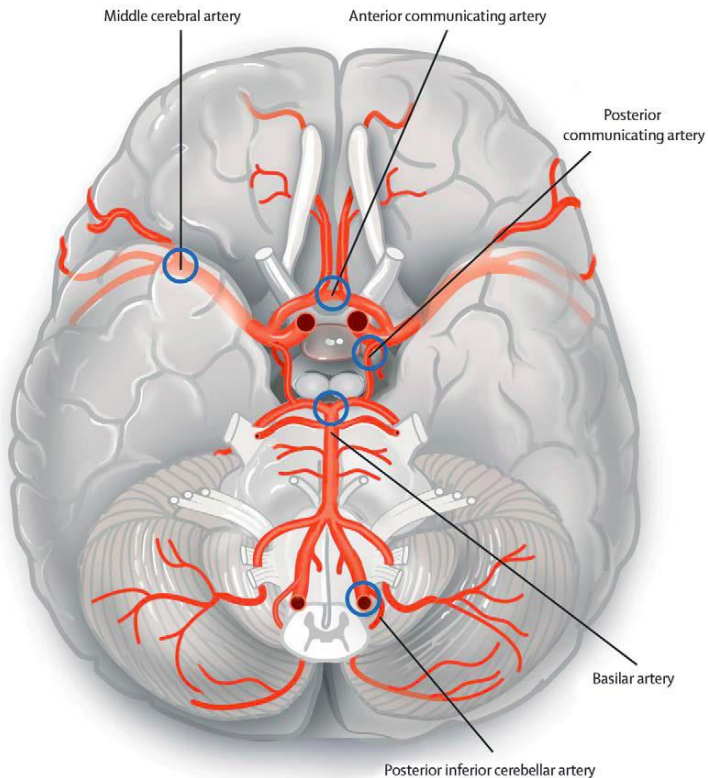


# Hemorrhagic Stroke Subarachnoid Hemorrhage (SAH)

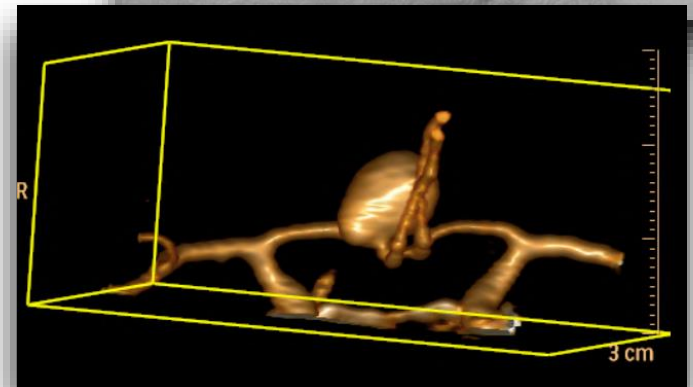
Bleeding into the subarachnoid space (extraaxial)

The most often cause – cerebral aneurysm rupture

The most often localization of aneurysm - Willis circle

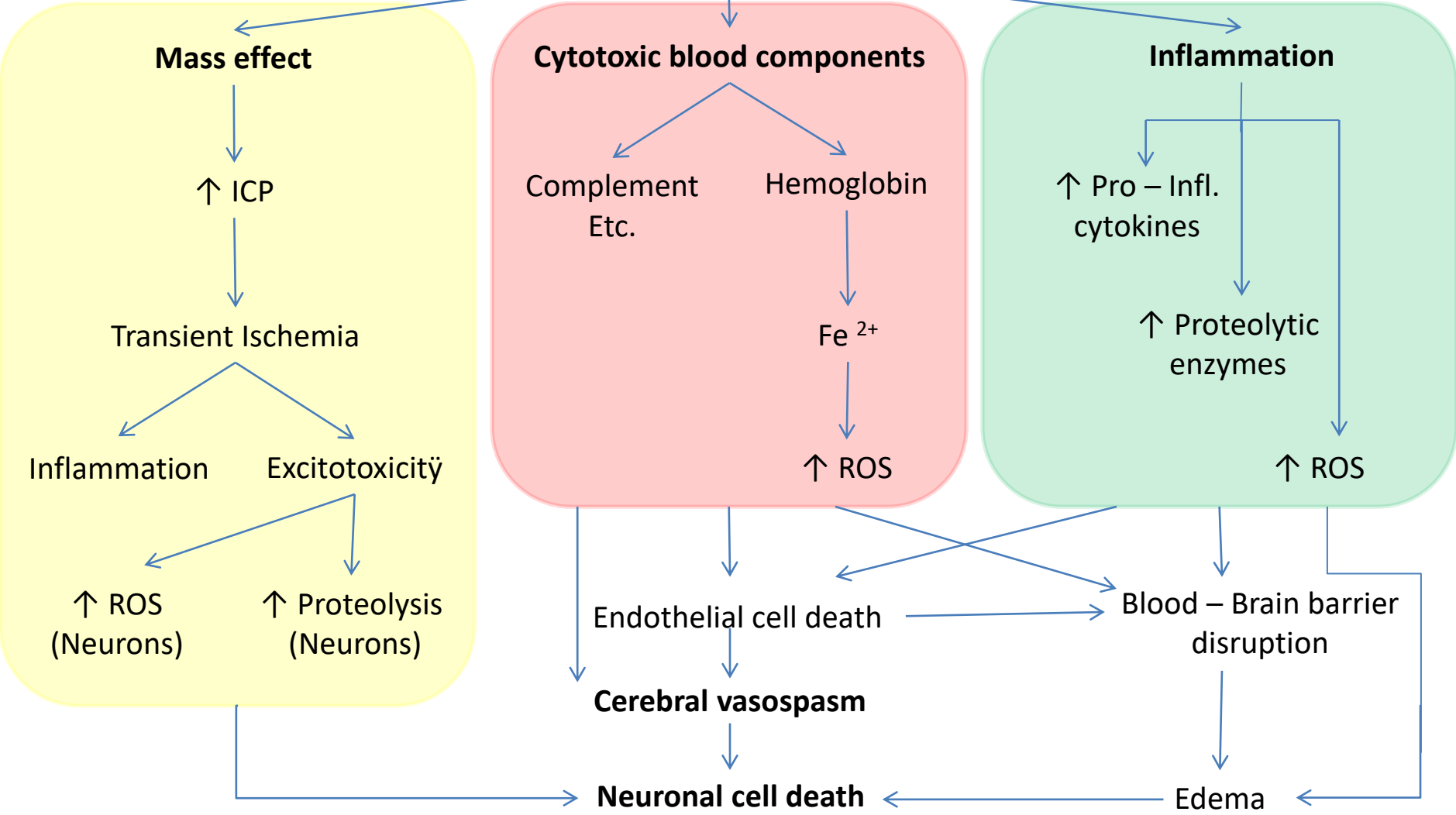


<http://chicago.medicine.uic.edu>



# Pathophysiology of SAH

Accumulation of blood in subarachnoid space





# **Traumatic Brain Injury**

# Traumatic Brain Injury

## Introduction

### The most often causes

- Traffic accidents
- Falls
- Sport injuries

### Classification

- Primary
  - ✓ Results from trauma...
- Secondary
  - ✓ Results from reactions initiated by trauma
- Focal
- Difuse

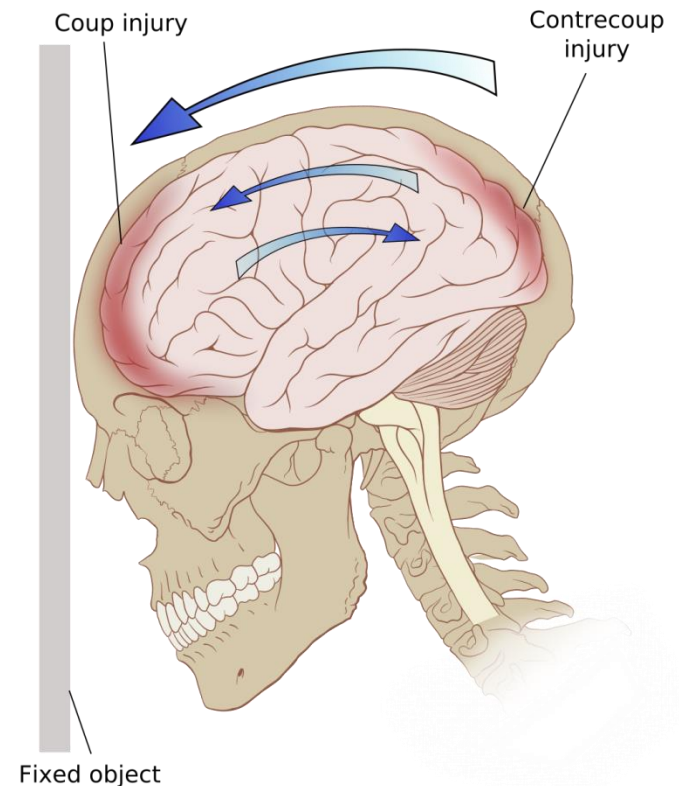
*Traumatic brain injury*  
*150 cases/ 100 000 persons*  
*The most often cause of death among*  
*people up to 45 years*



# Primary Brain Injury

## Mechanism of production

- **Contact injury**
  - ✓ Head hits the object or head is hit by the object
  - ✓ Risk skull fracture
    - ❖ Impressive – small objects
    - ❖ Linear – big objects
  - ✓ Gunshot injury
- Par coup injury
  - ✓ Contusion close to impact site
- Par contre coup
  - Contusion opposite to impact site
- **Noncontact injury**
  - Acceleration – deceleration injury



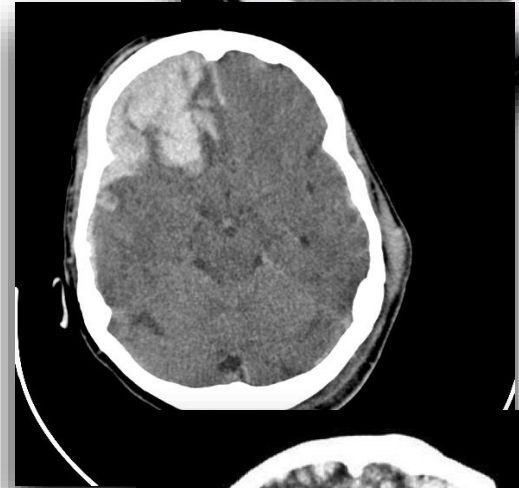
# Focal injury

## Contusion

- Mechanical damage of brain tissue, pia – arachnoid membranes not damaged
- Smooth transition between contusion and ICH
- The most often localizations
  - ✓ Frontal lobe
  - ✓ Temporal lobe

## Laceration

- The most severe grade of contusion
- Mechanical damage of both brain tissue and pia-arachnoid membranes
- Contusion + traumatic subarachnoid (subdural) hemorrhage



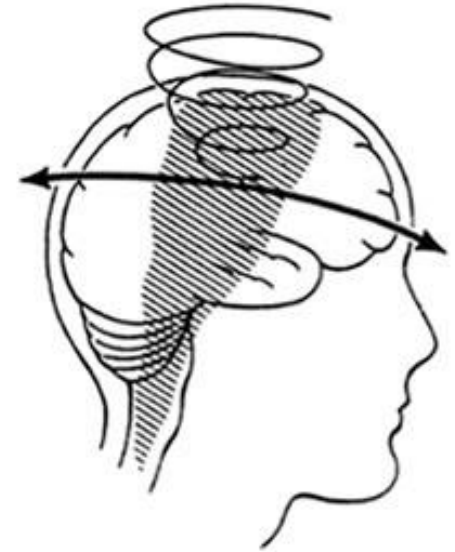
# Diffuse Brain Injury

## Diffuse axonal injury

- Structural damage of axons (white matter)
- Acceleration – deceleration, rotational forces
- No macroscopically detectable pathology
- Microscopically detectable axonal swelling
- Wallerian degeneration develops later
  - ✓ Degeneration of axon distally to injury
  - ✓ No axonal regeneration in CNS

## Concussion

- The mildest grade of diffuse axonal injury
- No structural tissue damage
- Transient functional damage (loss of consciousness not longer than 10 minutes)



# Secondary Brain Injury

## Edema

- Cytotoxic
- Vasogenic

## Ischemia

## Brain swelling

- Causes
  - ✓ Acidosis - vasodilatation
  - ✓ Diffuse microvascular injury
    - Vascular autoregulation failure
  - ✓ Damage brain areas responsible for vasoregulation
    - Thalamus, brain stem
    - Vasoparalysis

**Secondary injury results in ICP increase**

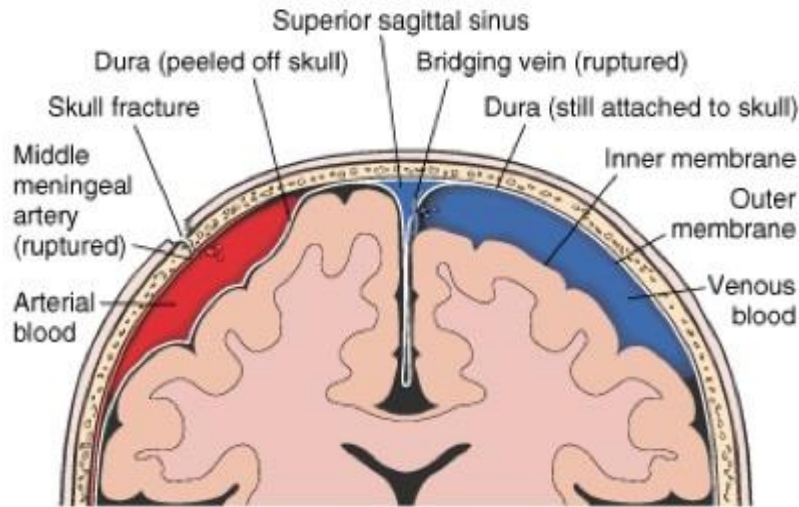
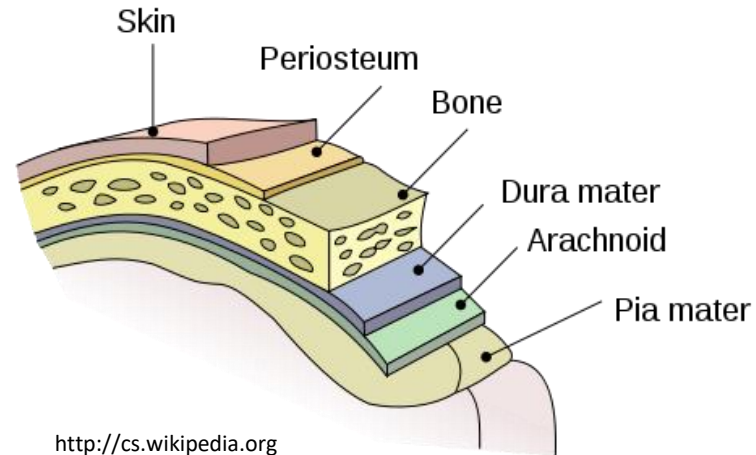
# Traumatic Hematomas

## Intraaxial

- Intracerebral

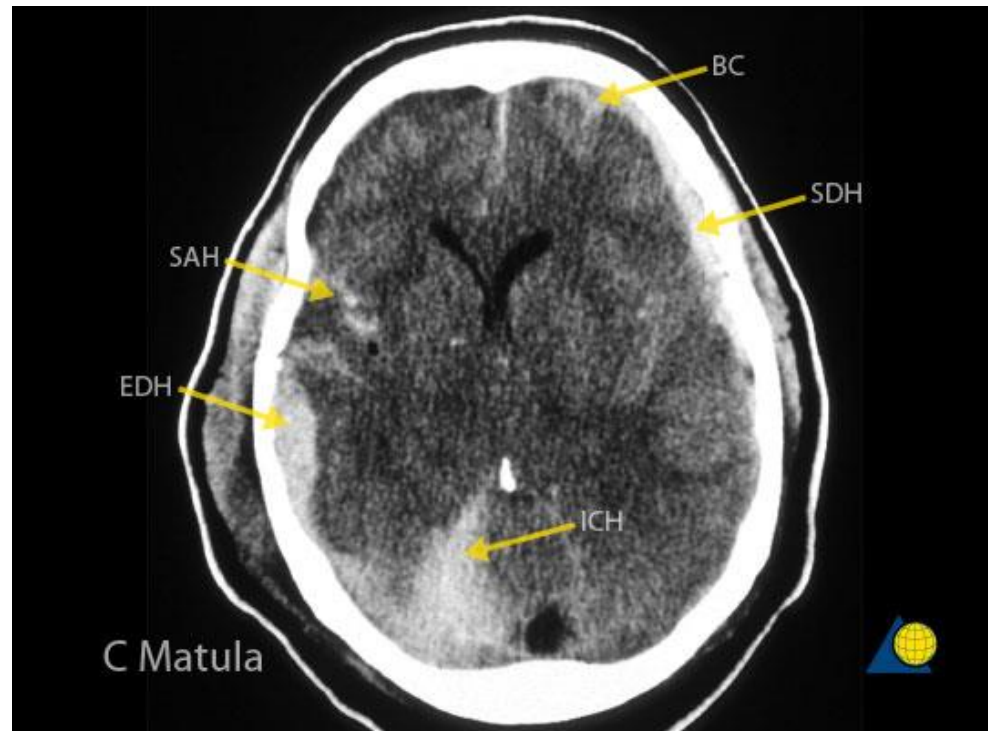
## Extraaxial

- Epidural
- Subdural
- Subarachnoid



A. Epidural hematoma

B. Subdural hematoma



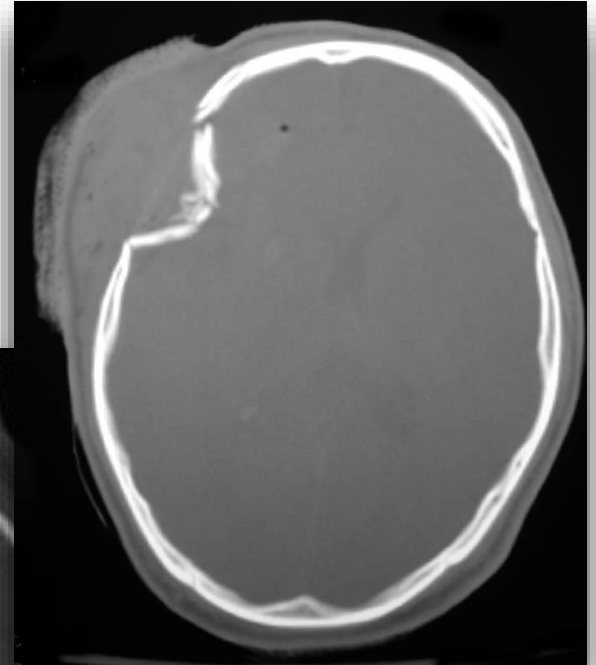
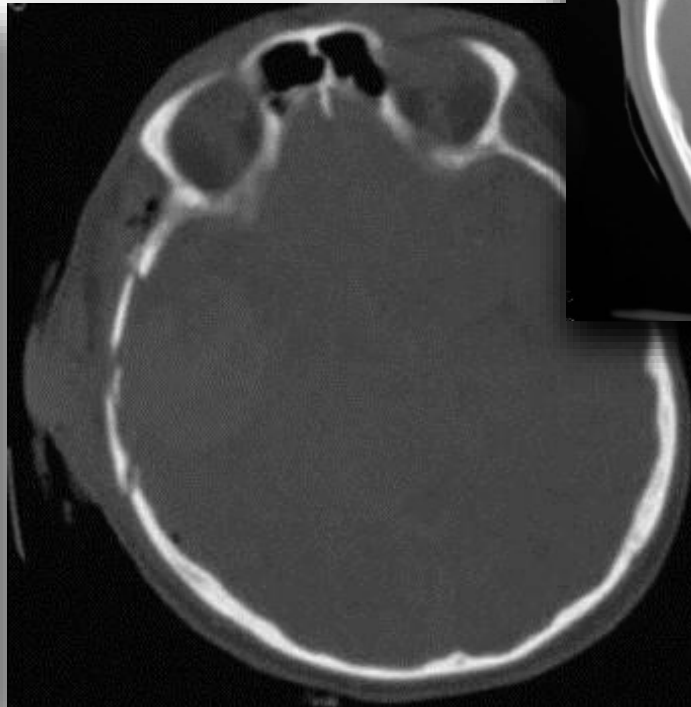
C Matula

# Intracerebral Hemorrhage

- Smooth transition between contusion and ICH according to severity of injury

## The most often localization

- Temporal lobe
- Frontal lobe



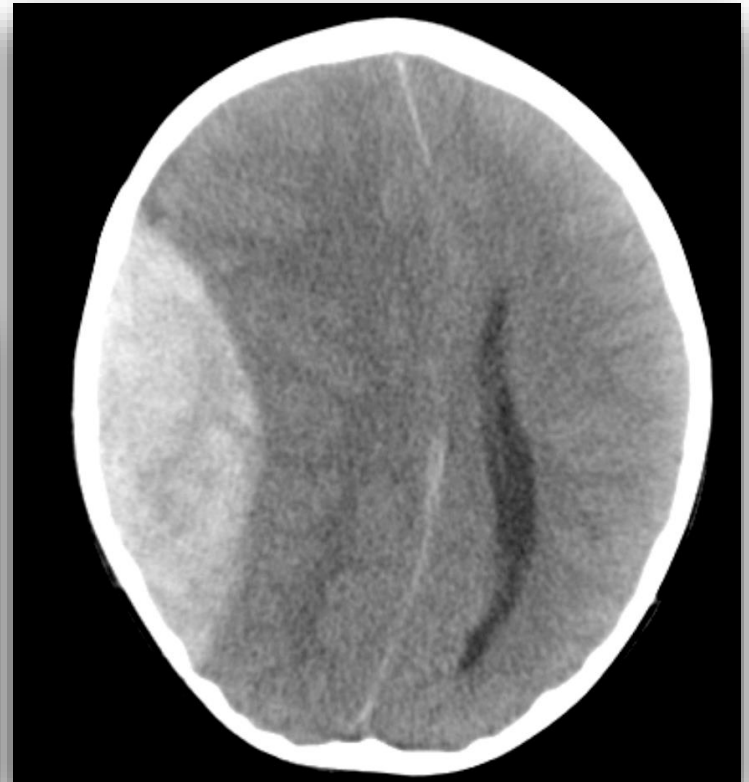
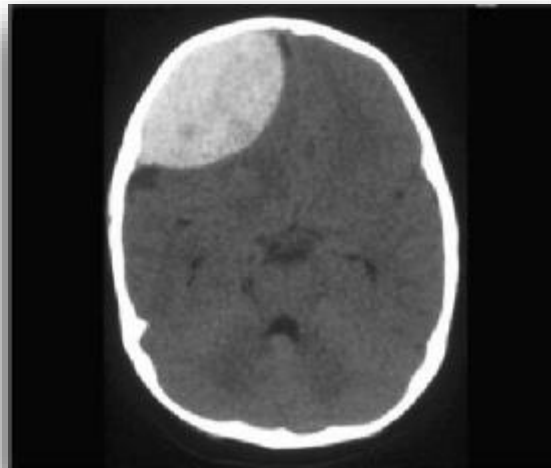


# Epidural Hematoma

- Blood collection between the skull and dura mater
- The most often cause is skull fracture, which leads to damage of meningeal artery (contact injury)
- Separation of dura from the skull – convex shape

## The most often localization

- Temporo - basal
- Temporo - parietal

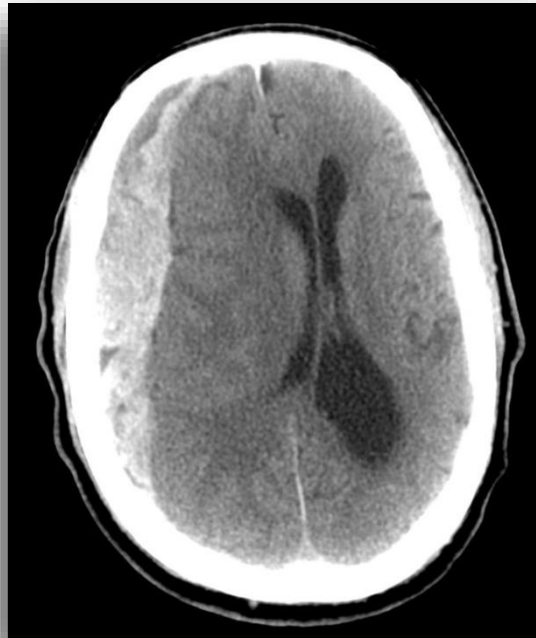


# Subdural Hematoma

- Blood collection between dura mater and arachnoidea
- The most often results from tears in bridging veins which cross subdural space (acceleration – deceleration injury)

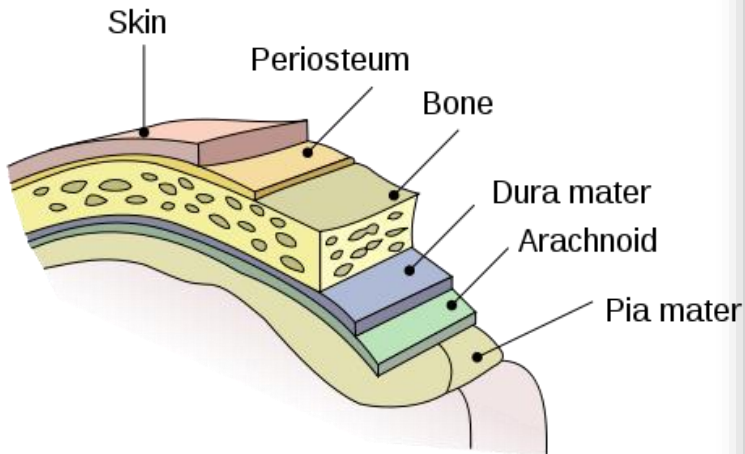
**Acute** – fresh blood

**Chronic** – colliquated blood

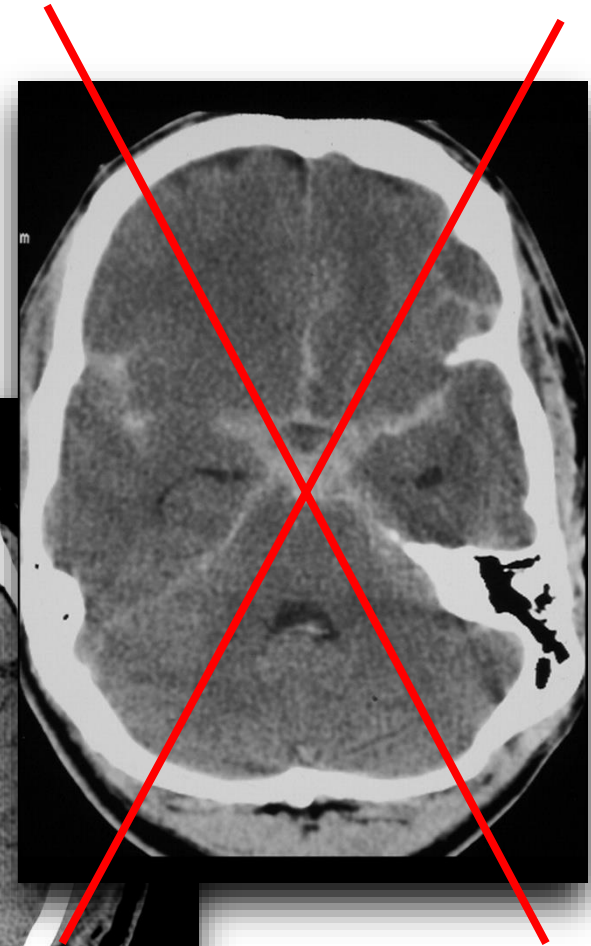
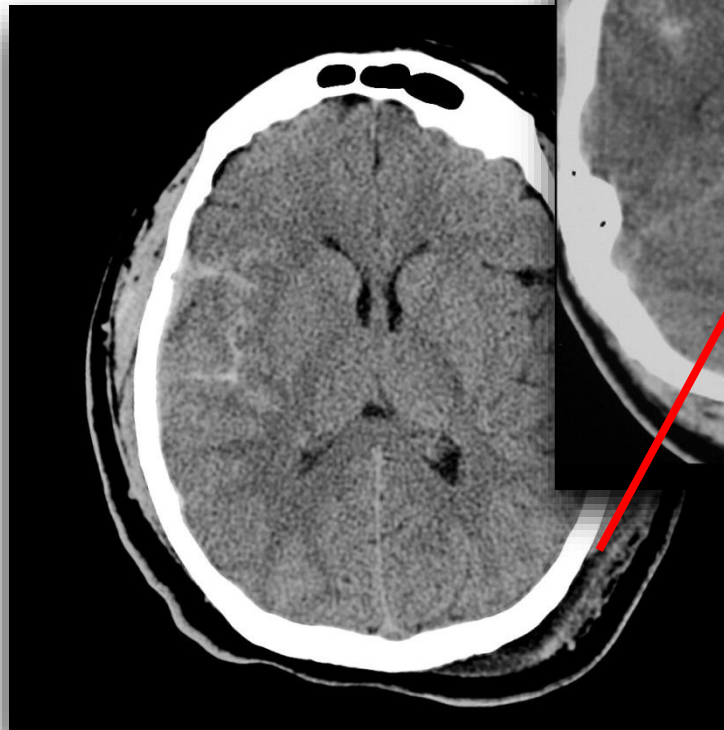


# Traumatic Subarachnoid Hemorrhage

- Blood collection between arachnoidea and pia mater
- Often associates with brain laceration
- No vasospasm occurs in traumatic SAH



<http://cs.wikipedia.org>



# Consequences of Brain Injury

- Impairment of consciousness
- Cognitive impairment (including executive functions)
  - Focal neurological deficit

## Impairment of Consciousness

### Qualitative

- Normal vigility, impairment of content
  - Disorientation

### Quantitative

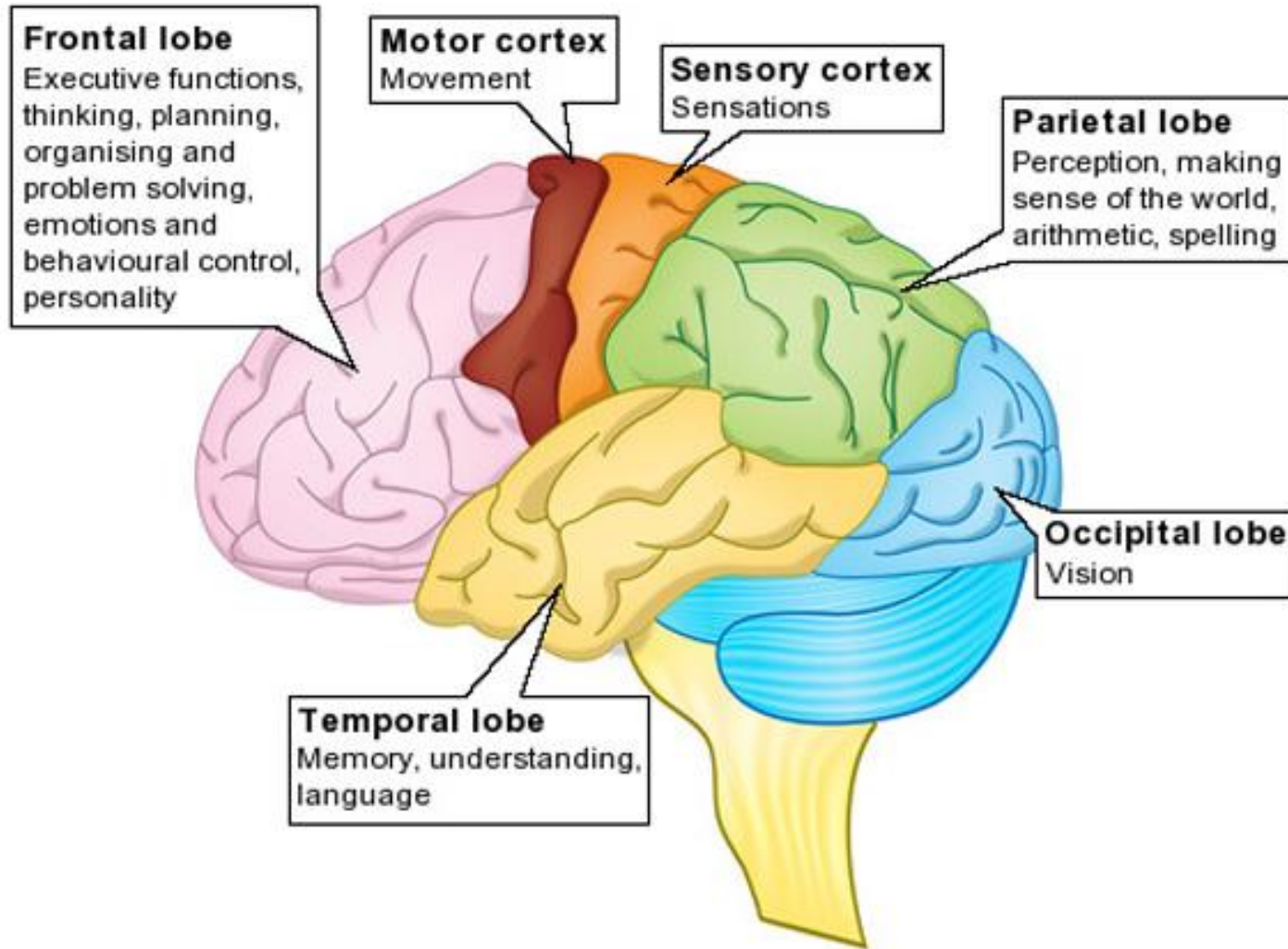
- Impairment of vigility
  - **Somnolence** – state of near-sleep, responsiveness
  - **Stupor** – responsiveness only to base stimuli (pain)
  - **Coma** - unresponsiveness

# Glasgow Coma Scale

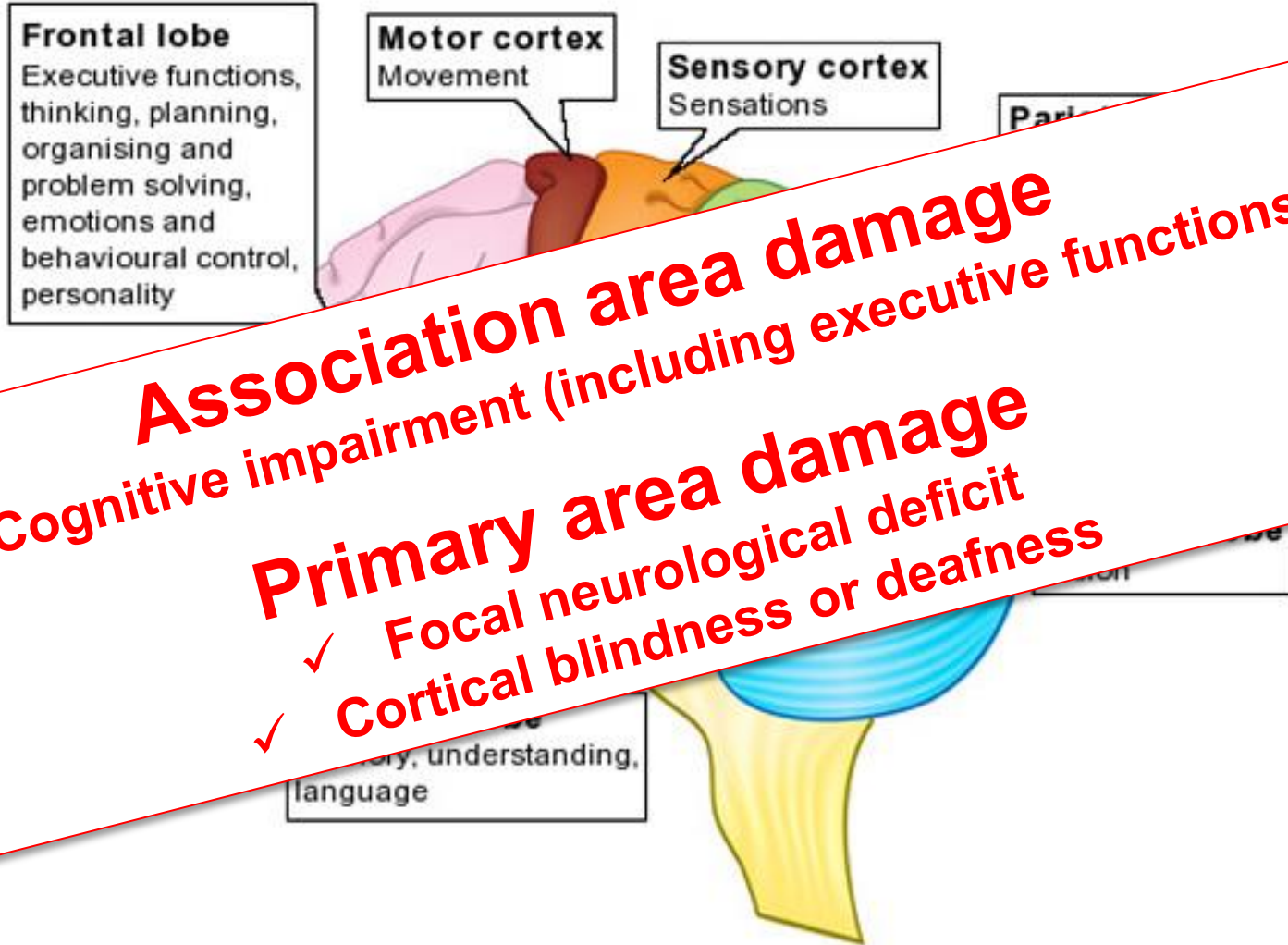
Best eye opening	Best verbal	Best motor
1 - None	1 - None	1 - None
2 – To pain	2 - Incomprehensible	2 – Extensor (decerebrate)
3 – To speech	3 - Inappropriate	3 – Flexion (decorticate)
4 - Spontaneous	4 - Confused	4 – Withdraws to pain
	5 - Oriented	5 – Localizes pain
		6 - Obeys

*Glasgow Coma Scale*  
 Normal consciousness: GCS 15  
 Mild brain injury: GCS 14 - 13  
 Moderate brain injury: GCS 12 - 9  
 Severe brain injury: GCS 8 - 3

# Cognitive Impairment and Focal Neurological Deficit



# Cognitive impairment and Focal Neurological Deficit



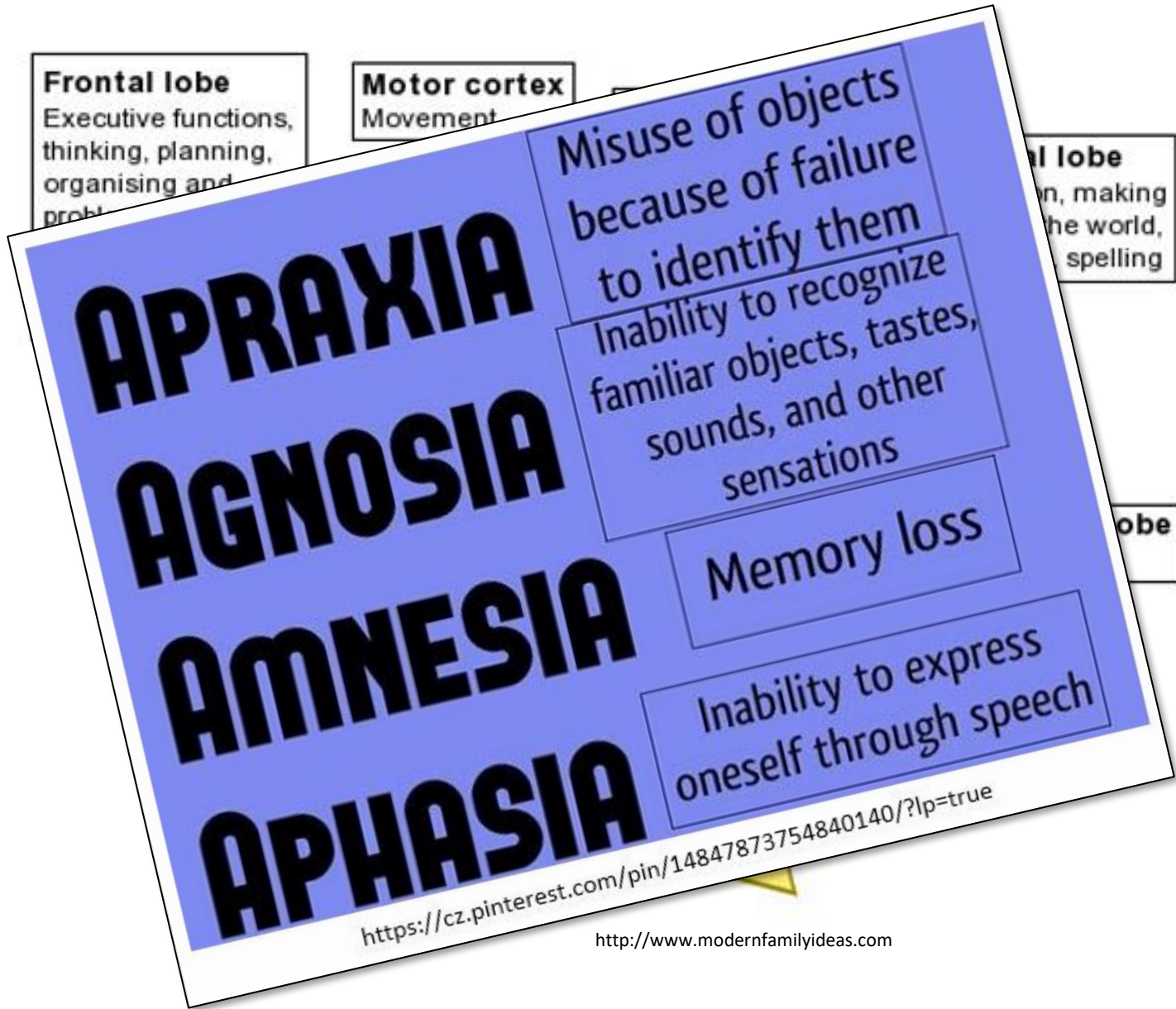
**Association area damage**  
✓ Cognitive impairment (including executive functions)

**Primary area damage**  
✓ Focal neurological deficit  
✓ Cortical blindness or deafness

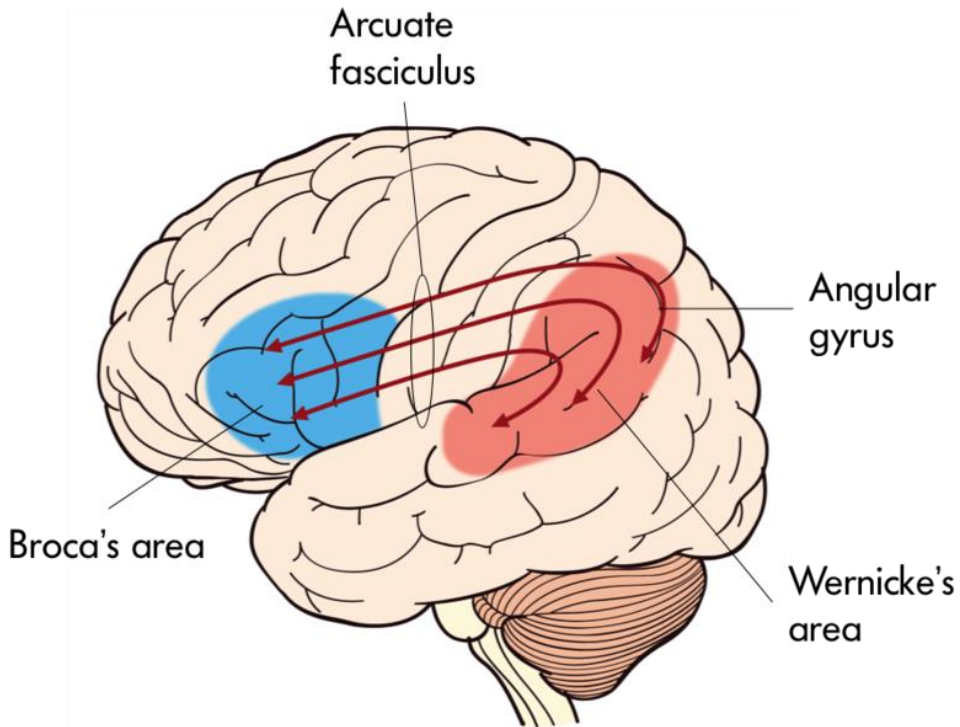




# „Dementia“ and Focal Neurological Deficit



# Language areas

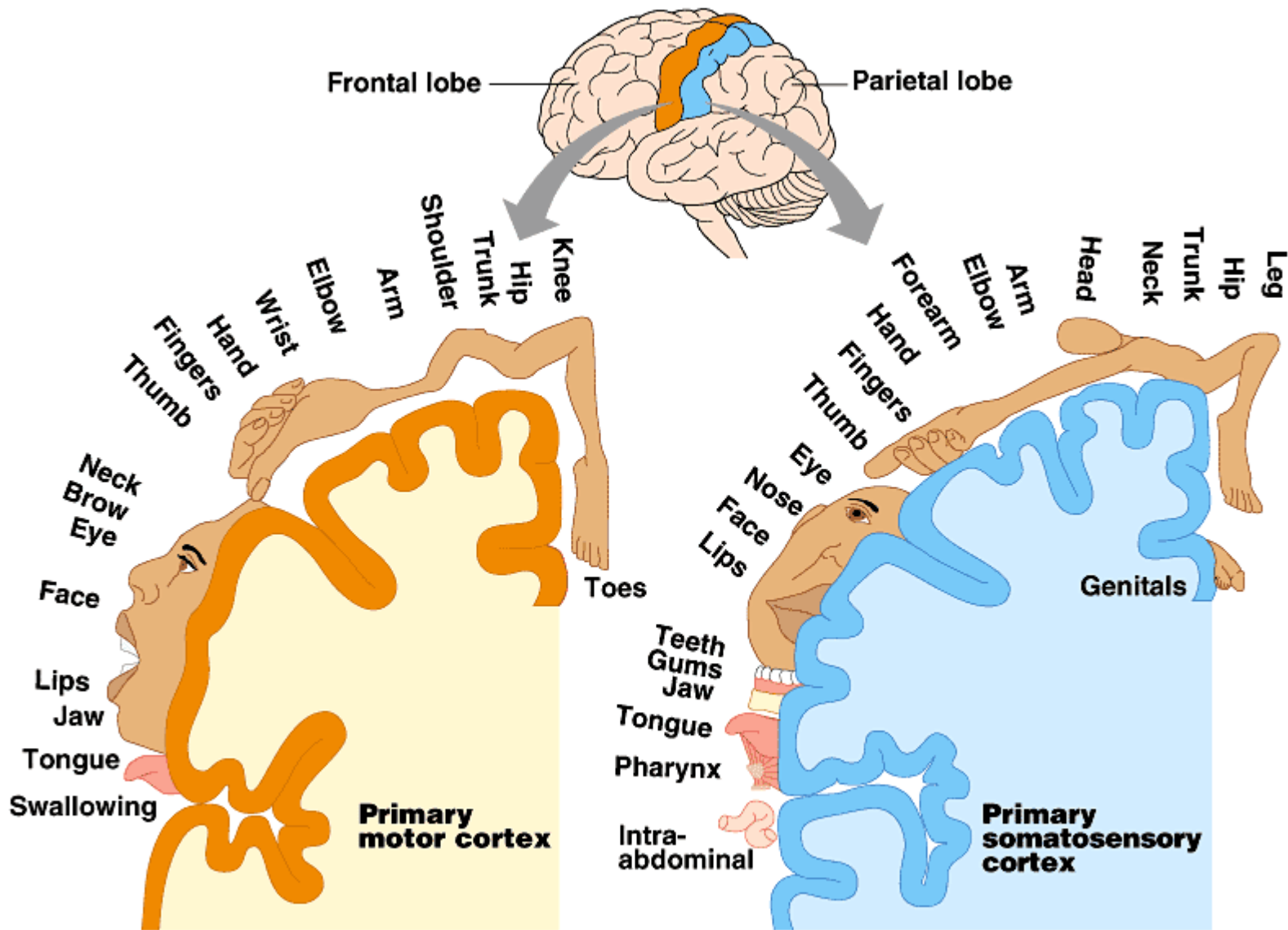


- Broca's aphasia
  - ✓ Motor, expressive
  - ✓ Comprehension preserved, speech unarticulated
- Wernicke's aphasia
  - ✓ perceptive, sensor
  - ✓ Comprehension damaged, speech fluent, but not meaningful

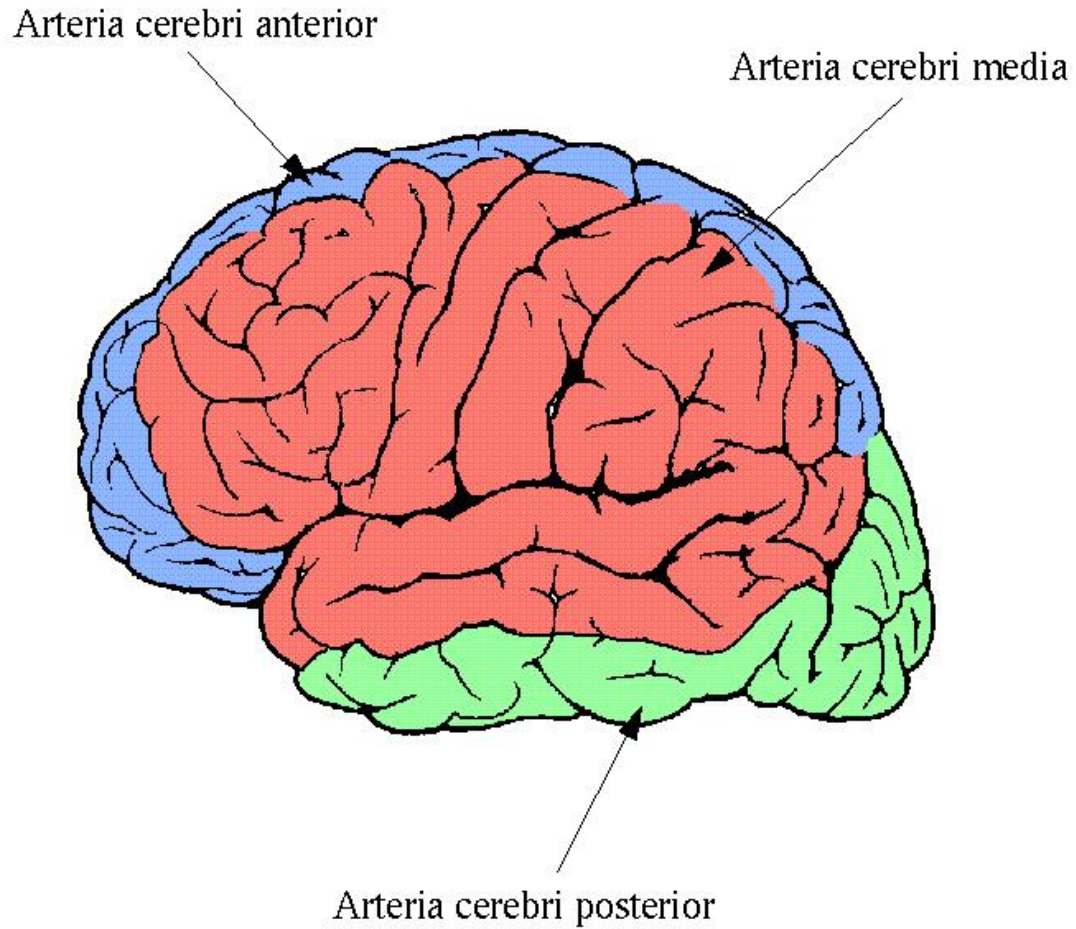
## There are two main language areas

- Broca's area (motor)
  - ✓ Close to motor cortex
- Wernicke's area (sensor)
  - ✓ Close to auditory cortex
- Fasciculus arcuatus
  - Conduction aphasia
    - ✓ Damage of fasc. arcuatus
    - ✓ Speech fluent, comprehension preserved
    - ✓ Problem with repeating words and sentences
  - Dysarthria
    - ✓ Problem with articulation
    - ✓ For example, damage of vocal cord

# Focal Neurological Deficit



# Focal Neurological Deficit



# Focal Neurological Deficit

## Examples of Ischemia

### Arteria cerebri anterior

- ✓ Contralateral hemiparesis accentuated on lower limb (FL)
- ✓ Behavioral impairment- bilateral occlusion (FL)

### Arteria cerebri media

- ✓ Contralateral hemiparesis accentuated on upper limb (FL)
- ✓ Impairment of speech functions – left side occlusion (FL, TL)
- ✓ Impairment of writing, counting, right – left orientation (TL)
- ✓ Impairment of spatial orientation when non-dominant parietal lobe affected

### Arteria cerebri posterior

- ✓ Impairment of vision (OL)
- ✓ Reading disorders (Corpus callosum, PL)

### Vertebrobasilar arteries

- ✓ Cerebellar symptomatology
- ✓ Brain stem symptomatology
  - ✓ Vertigo, nystagmus, diplopia, bilateral hemiparesis, paresis of cranial nerves respiratory disorders



# **Spinal Cord Injury**

# Spinal Cord Injury

## The most often causes

- Traffic accidents
- Work and sports injuries

## Mechanisms of injury

- Extensive Flexion, extension or rotation
- Direct impact

## Back injury

- Vertebrae
  - ✓ Fracture
  - ✓ Dislocation
- Ligaments
- Intervertebral disc

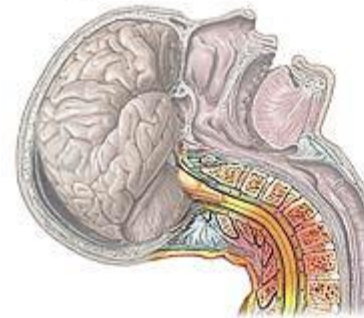
## Spinal cord injury

- Stretch
- Pressure

The most often localization of injury C4-C6 a Th11-L2

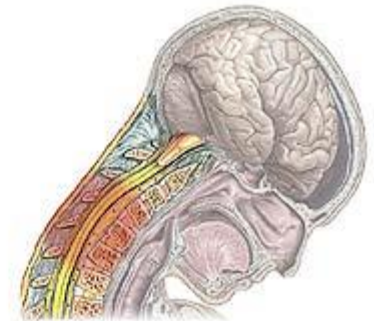
**Spinal Cord Injury**  
3-4 / 100 000 persons per year  
Almost 50% of patients are younger than 25 years

Hyperextension



Sprain or strain of cervical tissues

Hyperflexion



# Spinal Cord Injury

## Commotion

- Transient functional disability
- Reversible

## Contusion

- Incomplete spinal cord injury
- Complete spinal cord injury
  - ✓ Phase 1 – spinal shock
    - ❖ Areflexia and loss of descending facilitation distally from injury
    - ❖ Atony of urinary bladder detrusor with retention of urine and isshuria paradoxa
  - ✓ Phase 2 – spinal automatism
    - ❖ Hyperreflexia/spasticity distally from injury, loss voluntary motoric activity and loss of descending facilitation
    - ❖ Spasticity of urine bladder



# Consequences of Spinal Cord Injury

## Paralysis

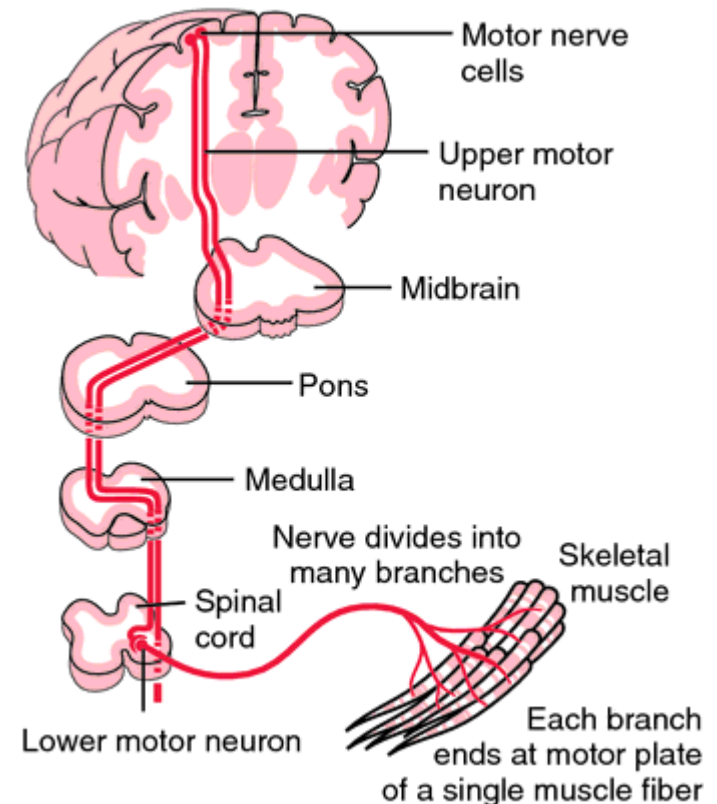
- Loss of muscle function most often caused by damage of nervous system

### Plegia

- Total paralysis

### Paresis

- Partial paralysis
- Mono-, di-, quadru-, para-, hemi-
- **Central**
  - ✓ Loss of upper motor neuron
  - ✓ First flaccid
    - ❖ Spinal shock
  - ✓ Then spastic
    - ❖ Activity of lower motor neuron
- **Peripheral**
  - ✓ Loss of lower motor neuron
  - ✓ Flaccid



# Consequences of Spinal Cord Injury Paralysis

## Spinal cord (SC) and spine (S) segments

- **Upper cervical:** SC=S
- **Lower cervical and upper thoracic:** SC=S+1
- **Middle thoracic hrudní:** SC=S+2
- **Lower thoracic:** SC=S+3
- **Medulary cone:** L1 –L2

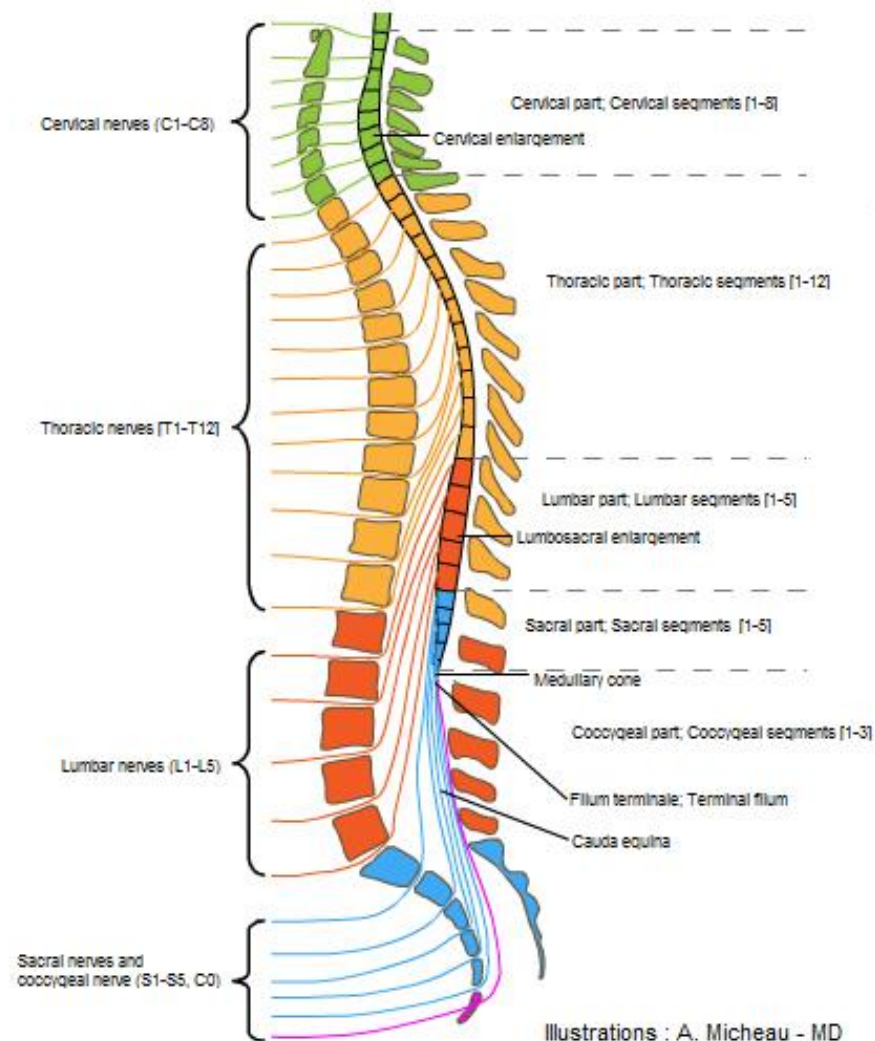
**Plexus cervicalis:** C1-C4

C4 – nervus phrenicus

**Plexus brachialis:** C5 – Th1

**Plexus lumbalis:** L1-L4

**Plexus sacralis:** S1-S5



Illustrations : A. Micheau - MD

<http://www.jhu.edu>

# Consequences of Spinal Cord Injury Paralysis

## C1 – C4

- ✓ Spastic quadriplegia
- ✓ Sphincter function disorders

## C5 – Th2

- ✓ Upper limbs: flaccid paresis/plegia
- ✓ Lower limbs: spastic paresis/plegia
- ✓ Sphincter function disorders

## Th3 – Th10

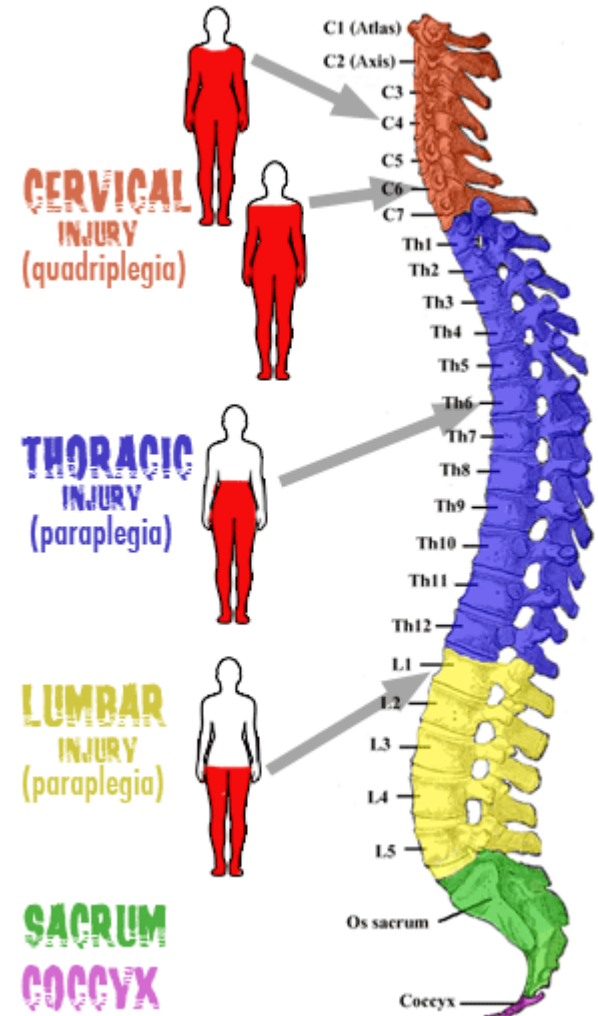
- ✓ Lower limbs: spastic paresis/plegia
- ✓ Sphincter function disorders

## Th9 – L2

- ✓ Lower limbs: flaccid paresis/plegia
- ✓ Sphincter function disorders

## L3 – S5

- ✓ Sphincter function disorders



# Consequences of Spinal Cord Injury

## Loss of sensation

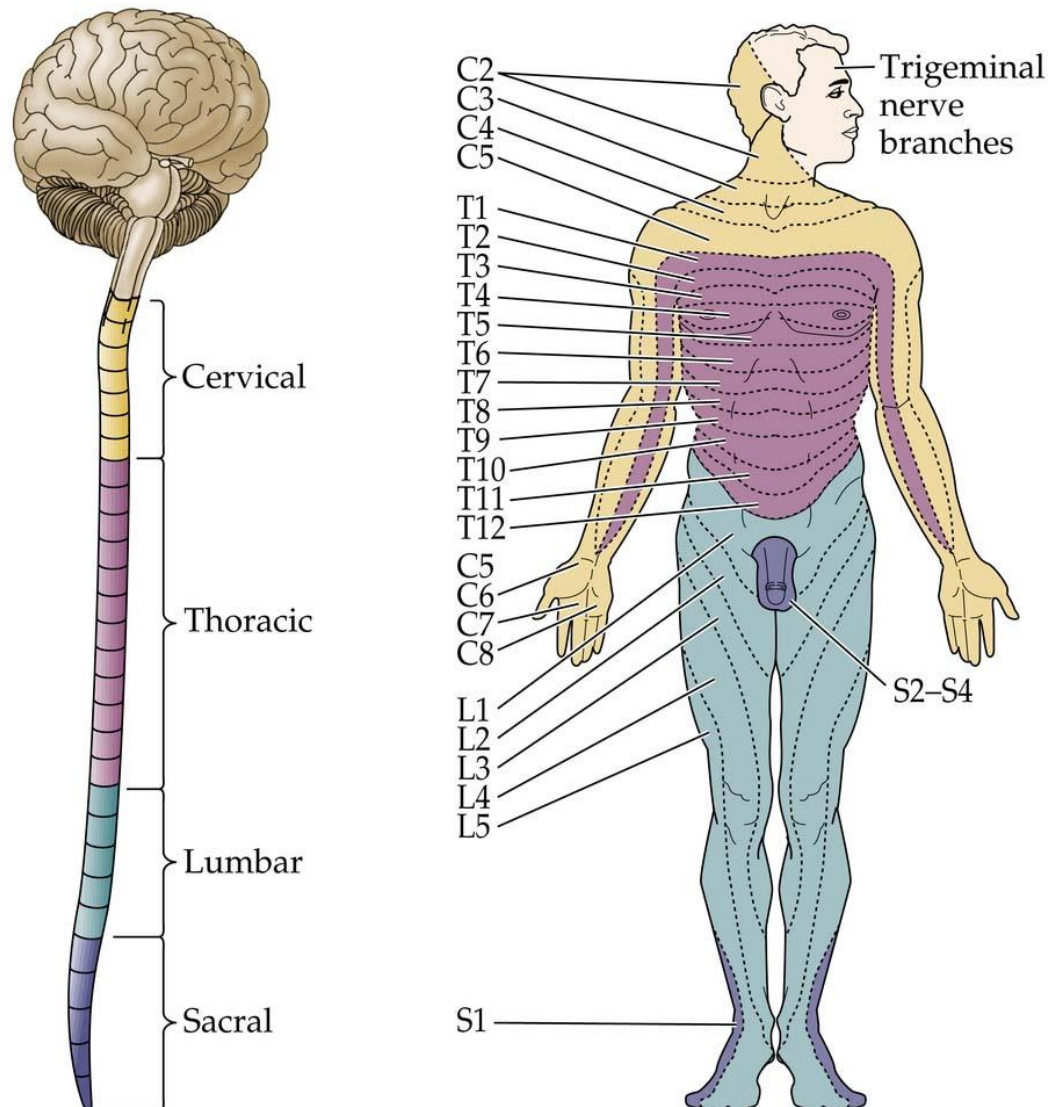
### Hypesthesia

- Incomplete loss of sensation

For example: Thermal hypesthesia, tactile hypesthesia

### Anesthesia

- Complete loss of sensation



**THANK YOU**

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