# Intracerebral hemorrhage

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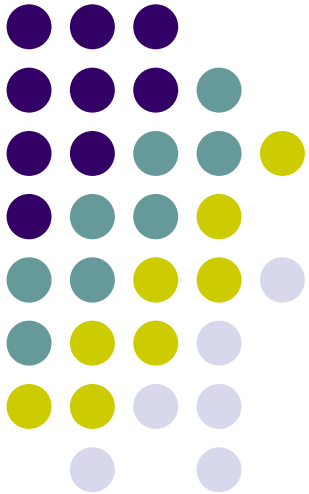

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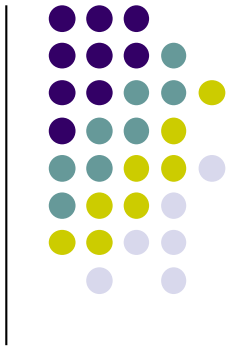
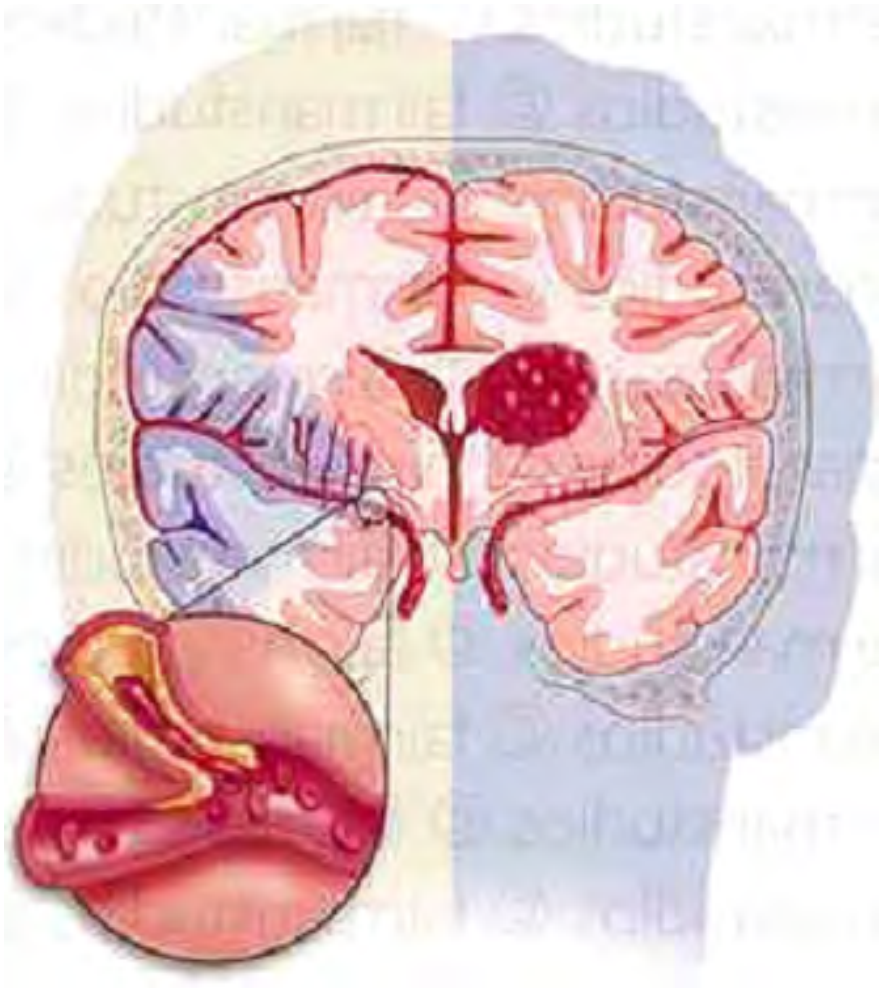
# Disclosures



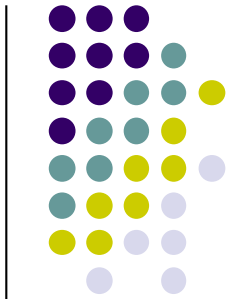
- consulting
  - CLS Behring, Bristol-Myers Squibb, Janssen
- PI in clinical trials
  - Boehringer-Ingelheim, Biogen, Bristol-Myers Squibb, Janssen, Penumbra, Portola, Medtronic
- European Stroke Organisation
  - Executive Committee

# Ischemic and Hemorrhagic Stroke



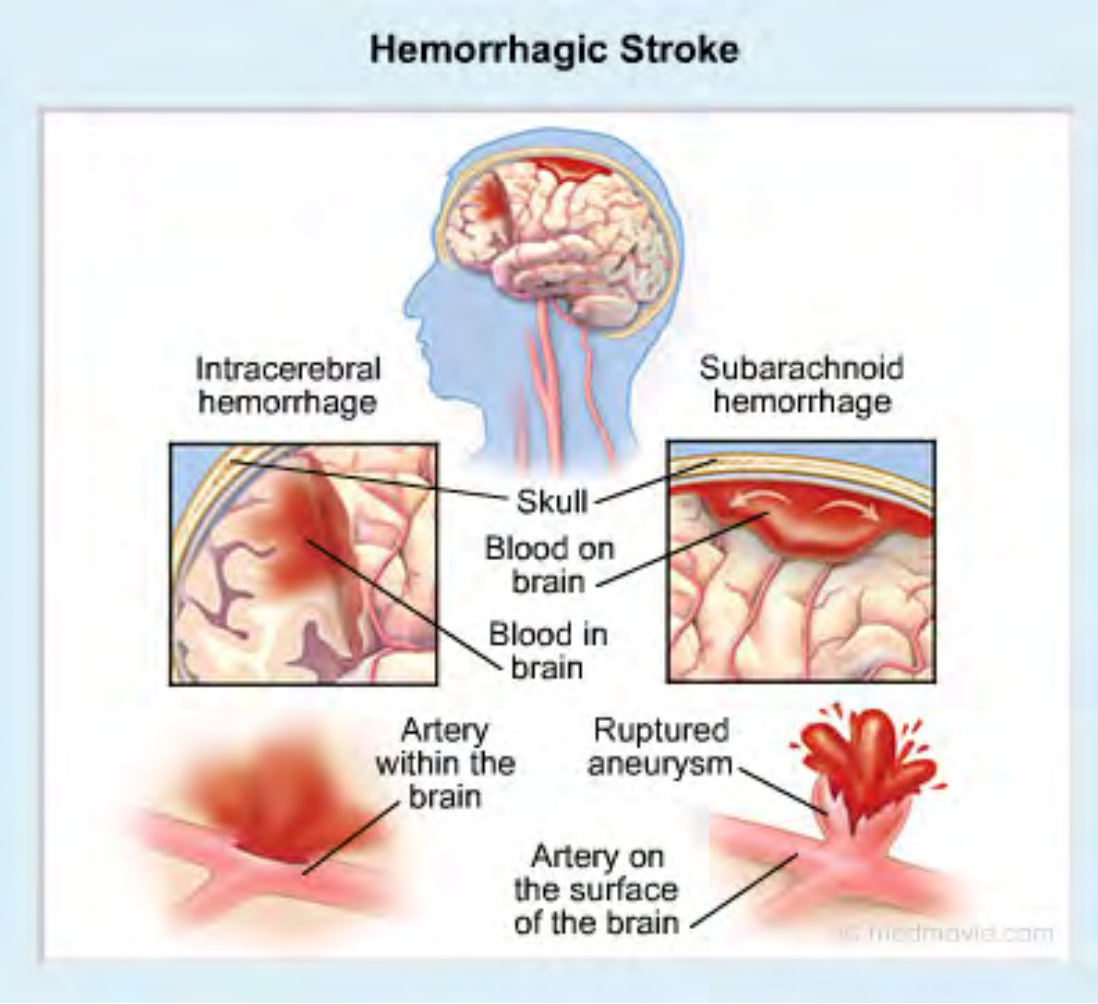
- leading cause of death and disability worldwide
- ~ 6% of health-care budget

# Worldwide statistics



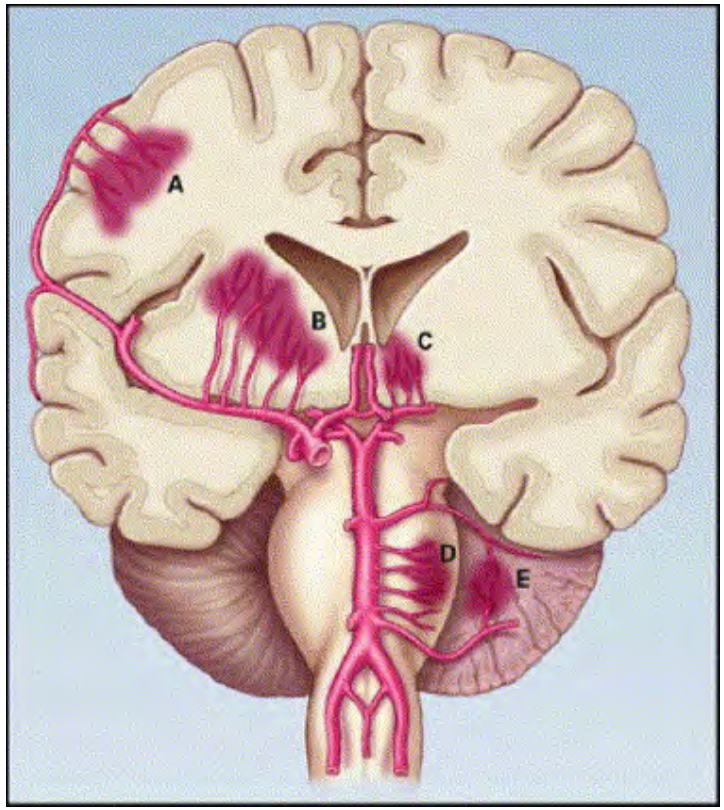
- 15 million people suffer stroke worldwide each year
  - 5 M die & 5 M are permanently disabled
  - High blood pressure contributes to over 12.7 million strokes
- Europe: approximately 650,000 stroke deaths each year
- In developed countries: the incidence of stroke is declining - largely due to efforts to lower BP and reduce smoking
- However, the overall rate of stroke remains high due to the aging of the population

# Hemorrhagic Stroke

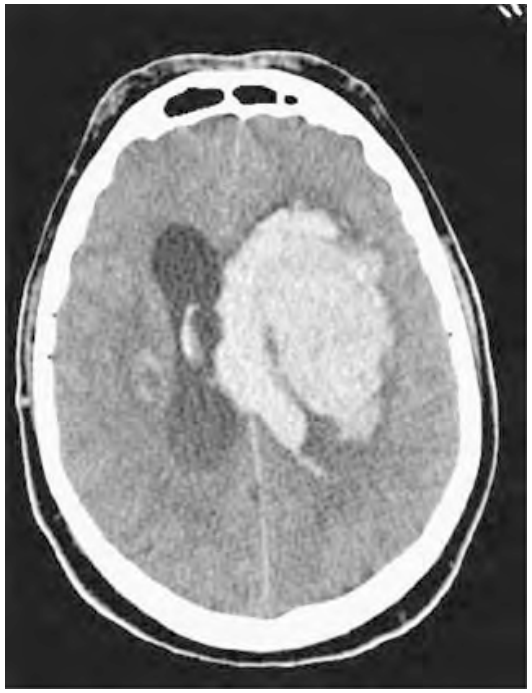



- intracerebral hemorrhage
  - 15% of all strokes
    - (~20-30% in Asians and Africans)
- SAH (~5%)

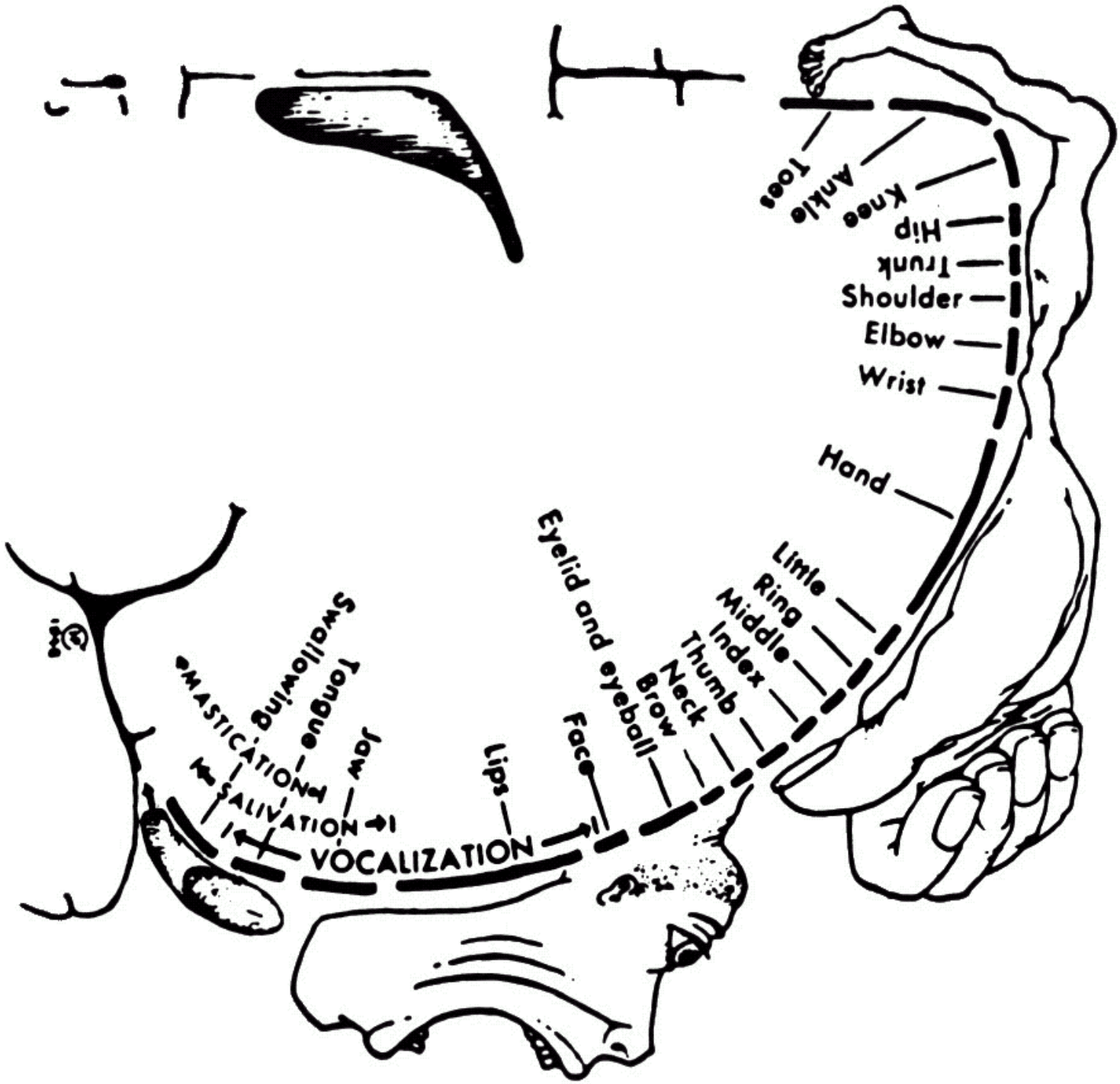
# Intracerebral Hemorrhage



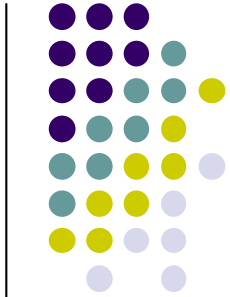

Qureshi AI et al. NEJM 2001



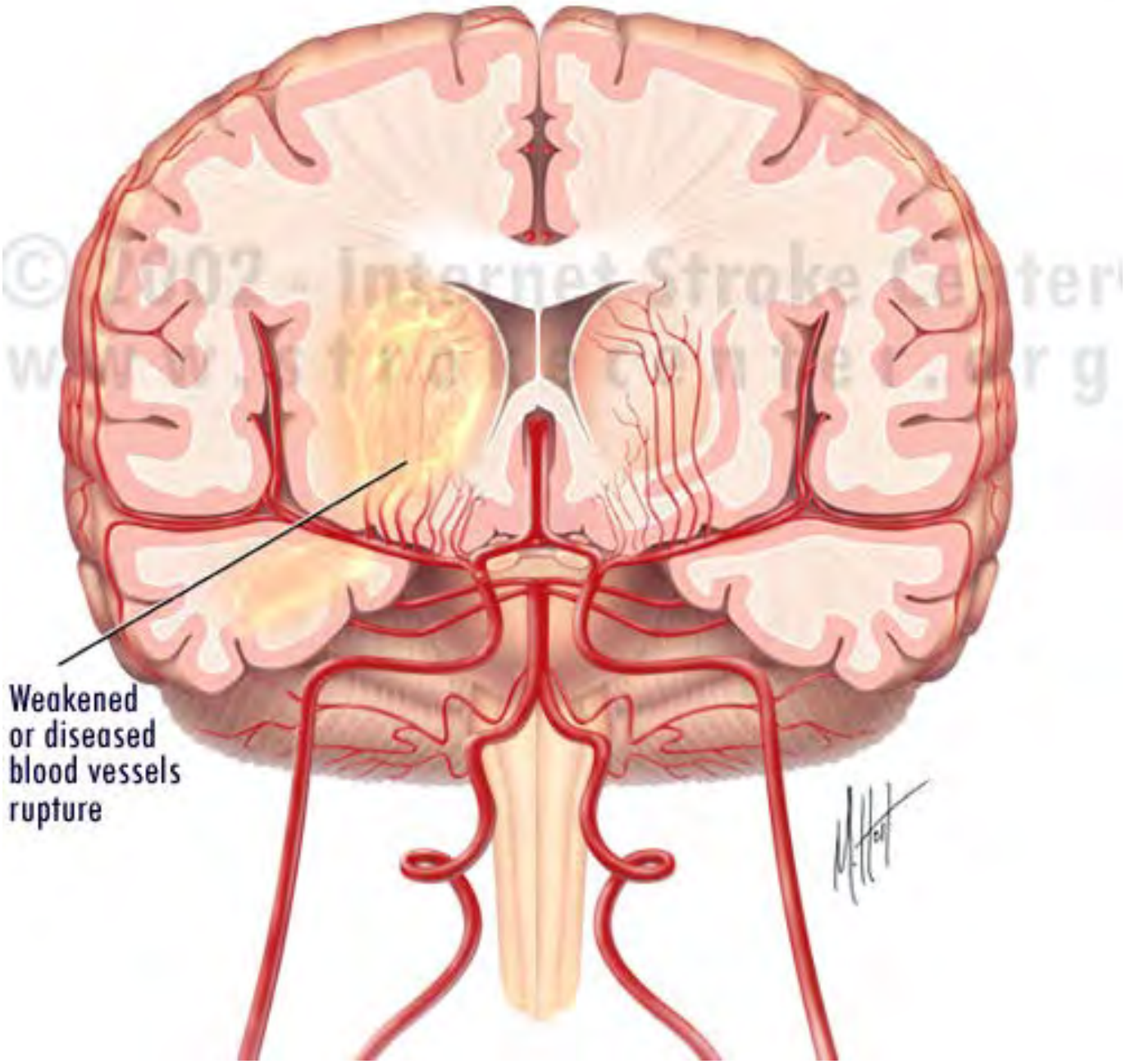
A: 19-25%; B: 35-44%;
C: 10-25%; D: 5-9%; E: 5-10%

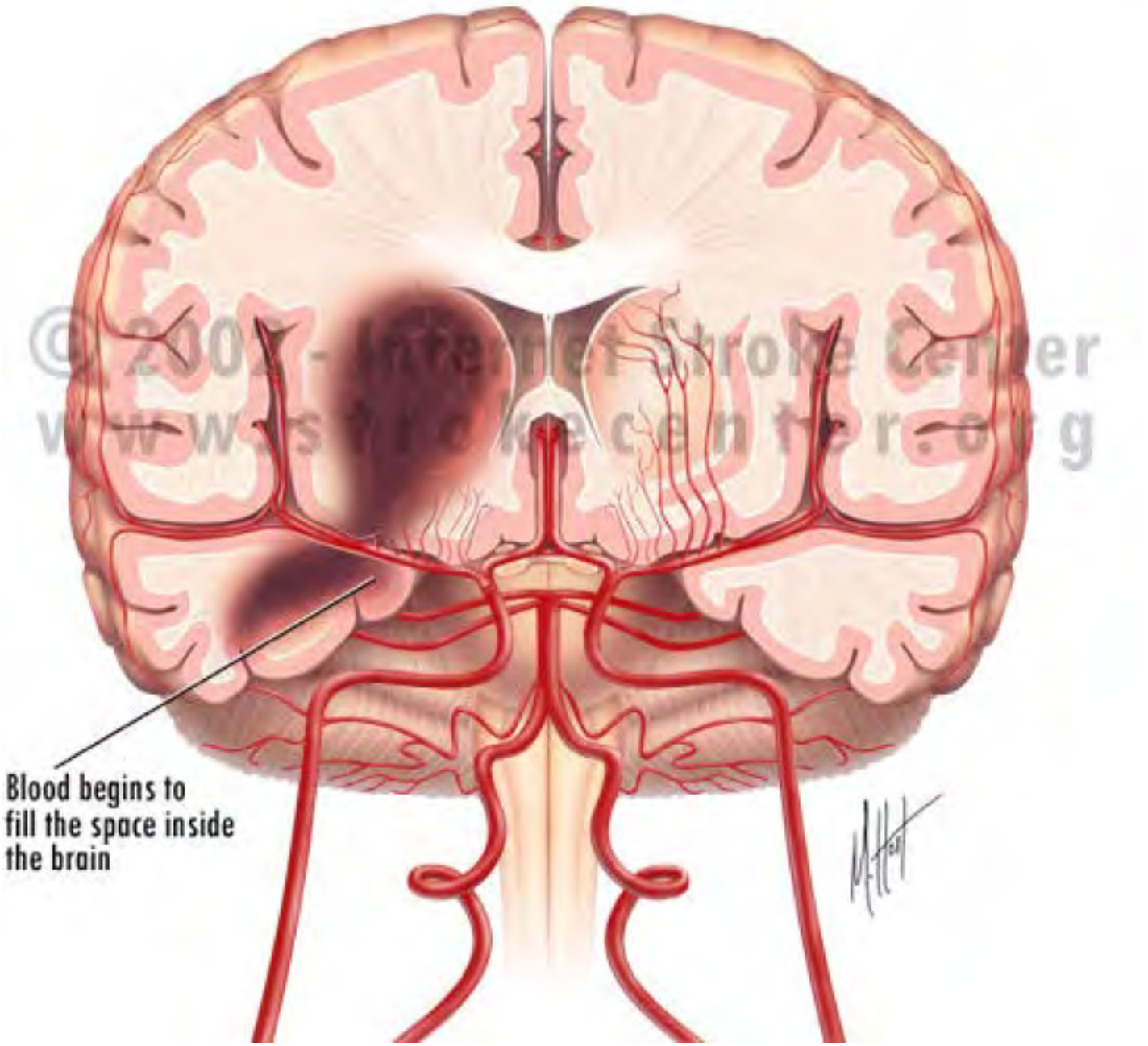

Toes
Ankle
Knee
Hip
Trunk
Shoulder
Elbow
Wrist
Hand
Little
Ring
Middle
Index
Thumb
Neck
Brow
Eyelid and eyeball
Face
Lips
Jaw
Tongue
Swallowing
MASTICATION
SALIVATION
VOCALIZATION

# Outcome

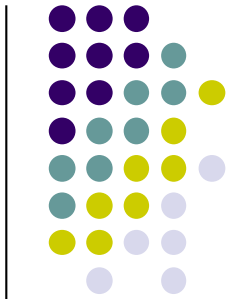


- 1-year mortality
  - ~50% (survivals disabled)
- large, deep hemorrhages
  - 3-month mortality ~95%


Weakened
or diseased
blood vessels
rupture


Blood begins to
fill the space inside
the brain

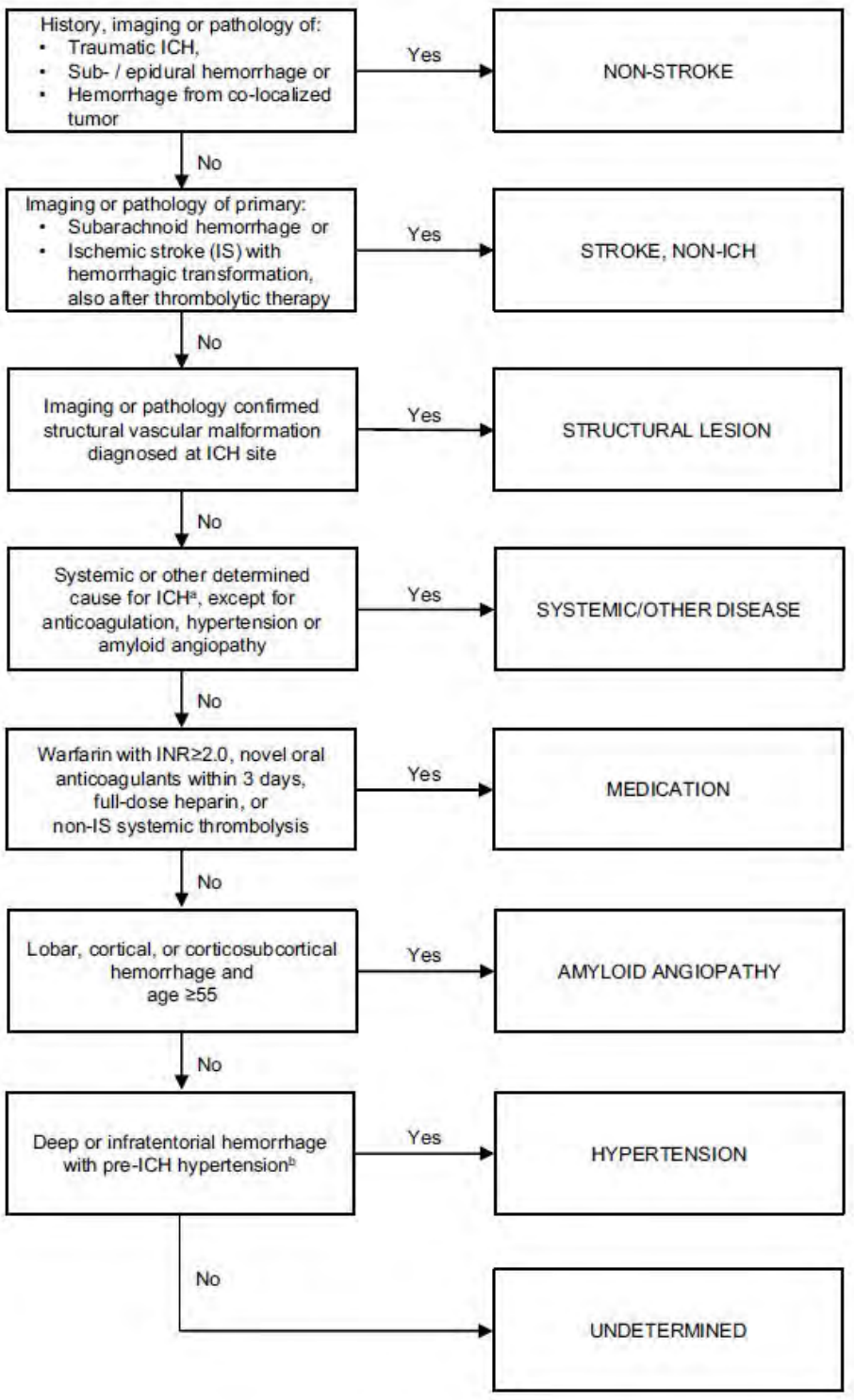
# Risk factors



- **High blood pressure**
- Cerebral amyloid angiopathy
- Weak areas in an artery wall (aneurysm)
- Abnormal connections between arteries and veins (arteriovenous malformation, or AVM)
- Cancer (breast, skin, and thyroid)
- Conditions or medications (such as aspirin or Warfarin) that can increase the chance of bleeding
- Use of illicit drugs such as cocaine

# Etiology

- SMASH-U

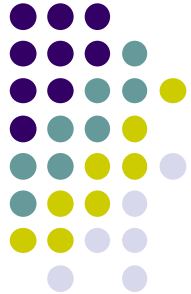



Meretoja A, Strbian D et al. Stroke 2012

# Dg

- anamnesis
- ECG
- lab packages, coagulation factors
- NCCT
- CTA
- MRI
- MRA (incl. venous phase)
- DSA
- histology

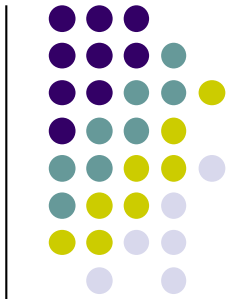
# Milestones of pathophysiology



- mass effect, ICP
- CBF, perihematomal penumbra ?
- hematoma growth + rebleeding
- edema and BBB leakage

- clot-derived factors
- hemoglobin breakdown products
- inflammation and complement
- mast cells

# Pathophysiology

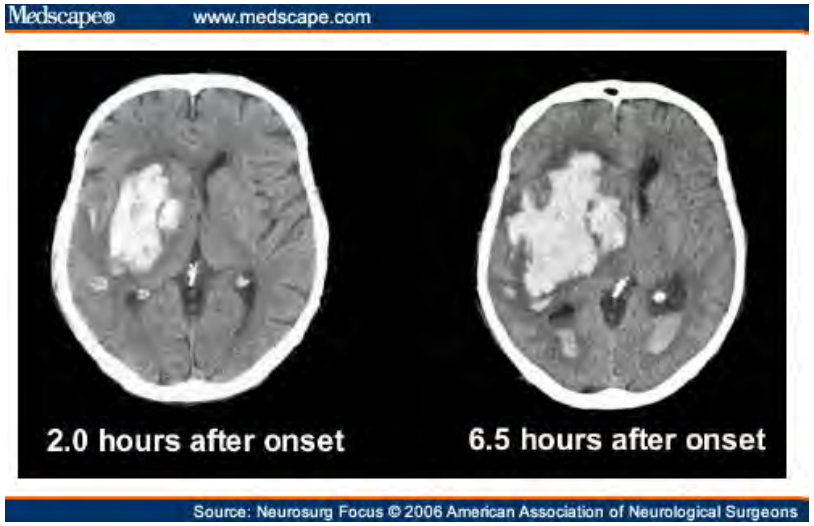


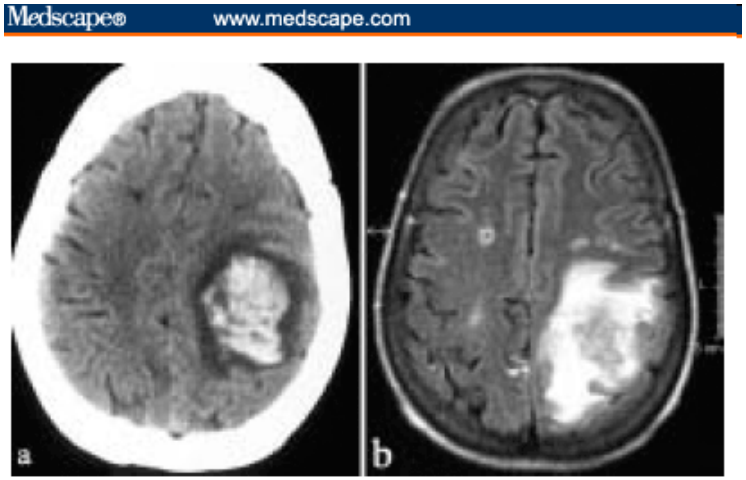
- mostly from experimental studies
- limitations of modelling
  - autologous blood injection vs. collagenase model
    - missing of ruptured vessel vs widespread dissolution of basal lamina + toxic effects of collagenase
    - hematoma growth
  - balloon inflation model – mechanical mass effect

- species-associated limitations in modelling
  - rodents: paucity of white matter
  - pigs: larger amount of white matter

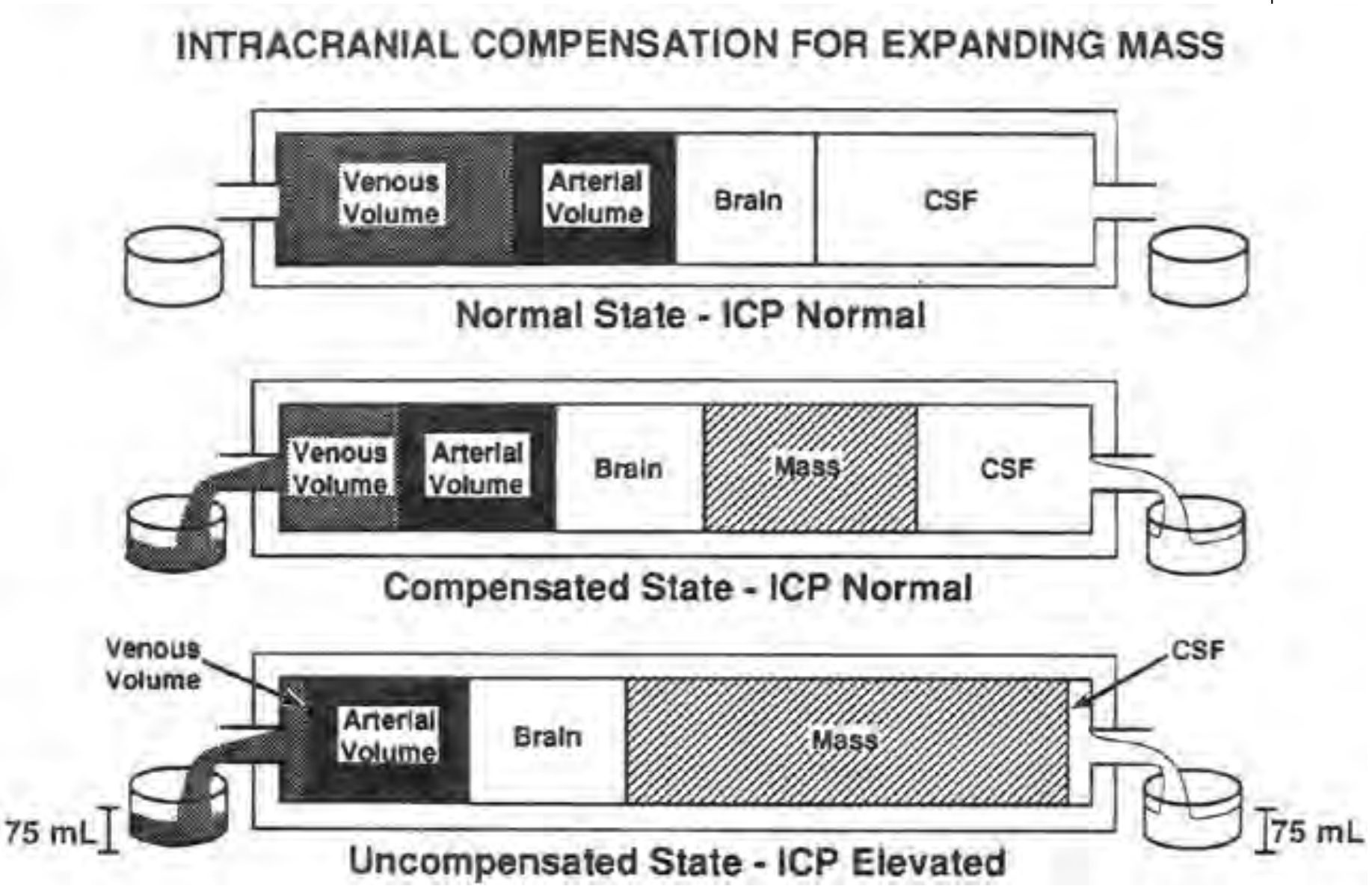
# Mass effect

- initial ictus
  - mechanical disruption of neurons and glia
- hematoma growth and rebleeding
- edema

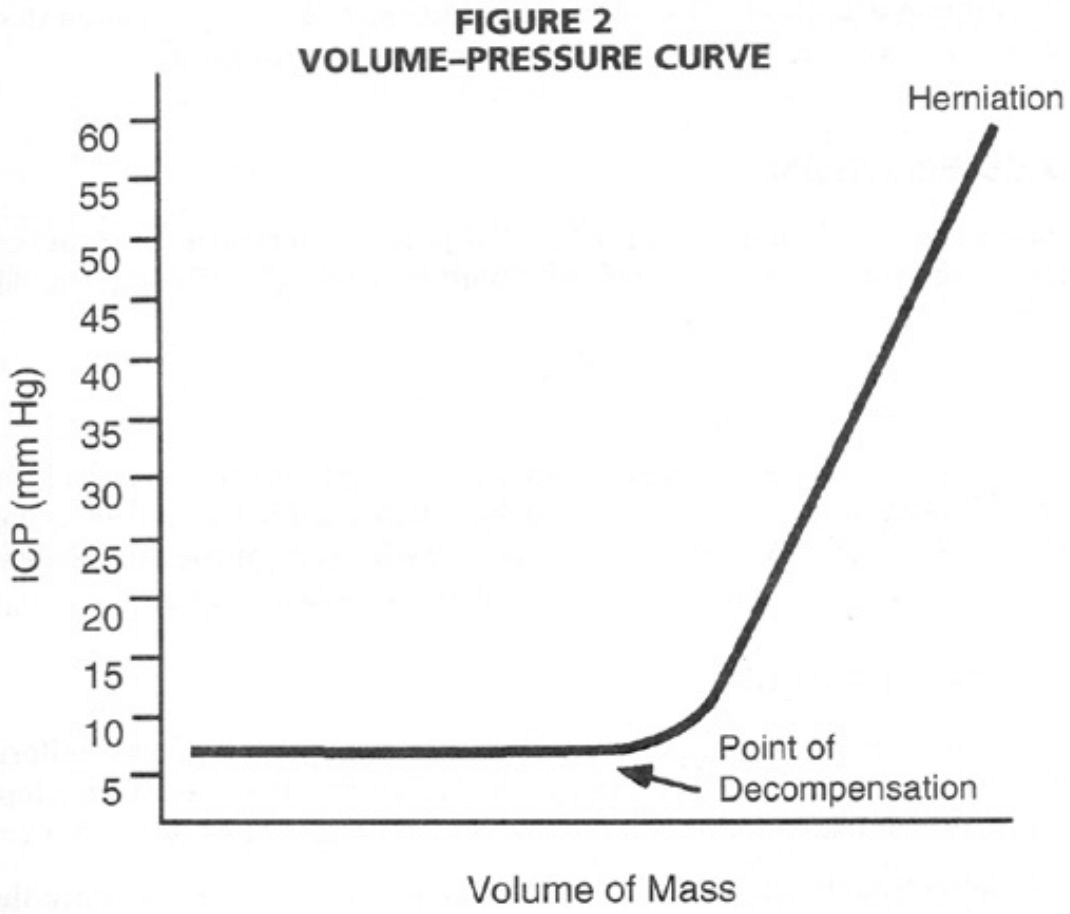


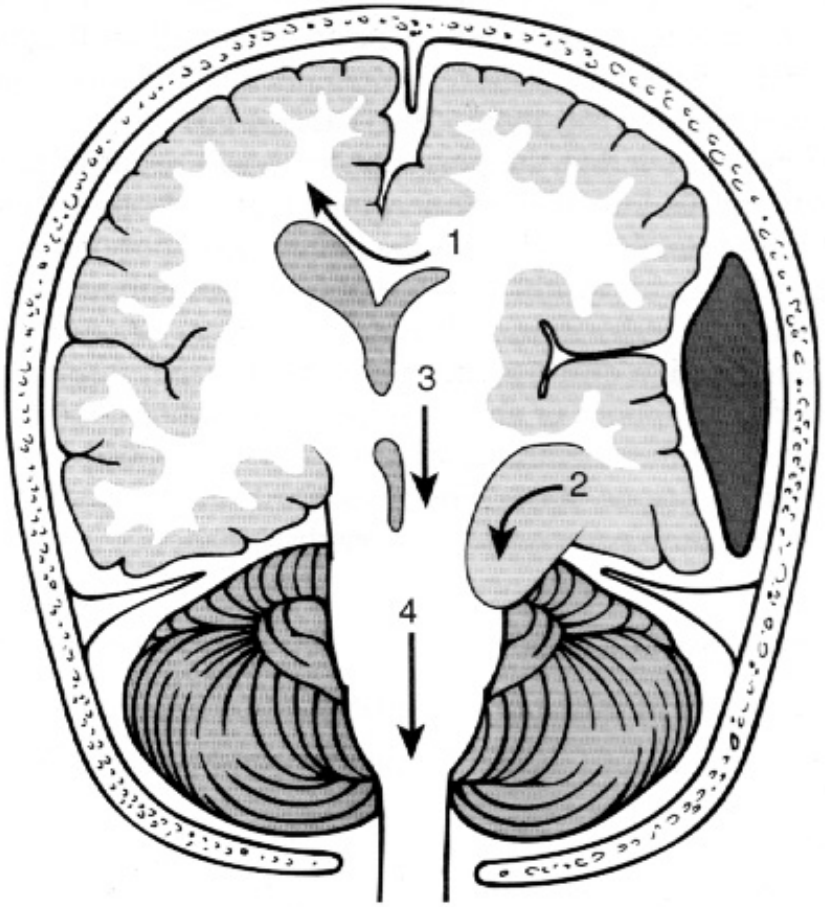



# Monro-Kellie Doctrine



# ICP, herniation

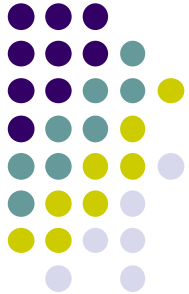


# Mortality by volume and localization

| | Deep | Lobar | Cerebellar |
|---|---|---|---|
| > 60cm$^3$ | 93% | 71% | - |
| 30-60cm$^3$ | 64% | 60% | 75% |
| < 30cm$^3$ | 23% | 7% | 57% |

# Perihematomal penumbra ?



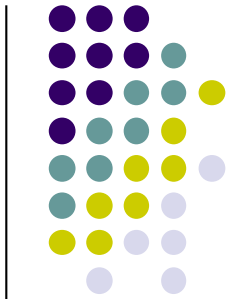
- mass effect of ICH – secondary ischemic injury
  - direct mechanical compression of the surrounding blood vessels
  - vasoconstrictor substances in the blood

- PET ($CMRO_2$, OEF, CBF) and DWI (ADC, rADC)
- hypometabolic and hypoperfusion (hibernation)
- hypoperfusion without ischemia
- metabolic failure
- mitochondrial dysfunction responsible for reduced metabolic demand

↑↑↑ ICP & ↓↓↓ CBF » » » global ischemia

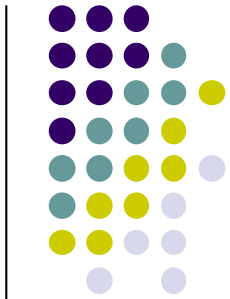
CPP = MAP - ICP

# Hematoma growth & rebleeding



- 2 retrospective studies: 14% / 22% within 24h
- prospective study: 38% of patients within 20h
- contributes to mass effect

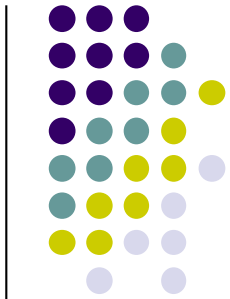
# Edema I



- experimental: within 1h after ICH, peaks around 3rd or 4th day
- human: develops within 3 h, increases by 75% within 24 h, peaks  around 5-6 d, and lasts up to 14 d

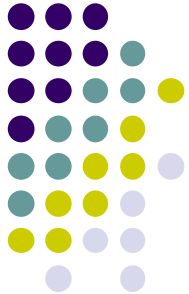
- relative edema volume (absolute edema volume relative to hematoma volume): predictor of outcome

# Edema II



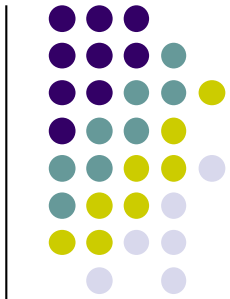
- hyperacute edema (< 24h)
  - oncotic pressure: serum proteins, glucose, electrolytes
- acute edema (24-72h)
  - cellular toxicity: WBC, platelets
  - humoral toxicity: IL-1, IL-6, TNF-α, PGs, LTs, VEGF, ICAM, complement
  - coagulation cascade: thrombin, fibrinogen
  - excitotoxicity: glutamate
- late phase (> 72h)
  - blood degradation products (Hb, Fe, biliverdin)
  - NO, free radicals, apoptosis, MMPs

# Blood-brain barrier damage



- intact for several hours after ICH
- modest disruption 12-24h later
- progressive disruption 48h later

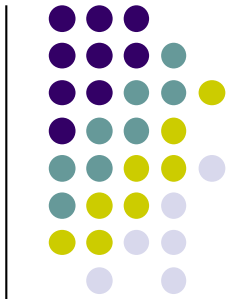
# Clot-derived factors I



- injecting various solutions into the basal ganglia, 24h follow-up
- edema induced by
  - whole blood HOWEVER NOT BY
  - concentrated blood cells
  - serum from clotted blood
  - plasma from unclotted blood HOWEVER
  - plasma + prothrombinase – edema induction AND
  - hirudin (thrombin inhibitor) reduced such edema

**THROMBIN**

# Clot-derived factors II

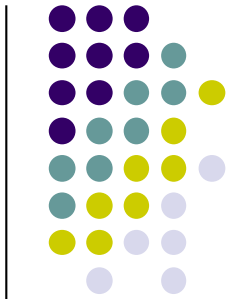


- injecting various solutions into the basal ganglia, 24h follow-up
  - whole blood – edema, blocked by thrombin inhibitor
  - artificial clot (styrene microspheres, fibrinogen, thrombin)
  - separately components of the artificial clot

the single component responsible for production of brain edema in all these models was thrombin

non-clotting heparinised blood does not result in edema: experimentally and clinically

# Hemoglobin breakdown products

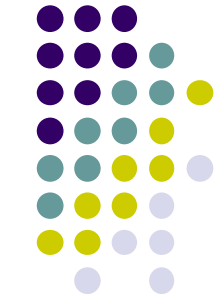


- infusion of packed RBCs – delayed edema 72 h later

- infusion of lysed RBCs – edema formation within 24 h

**HEMOGLOBIN**

# Inflammation and complement

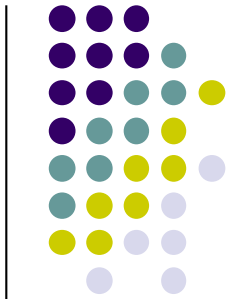


- rodents: neutrophil infiltration begins within 24h, peaks at 2 – 3 d, disappears between 3 -7 d
- T-Ly at 48 h up to 1 wk
- activated microglial cells evident at 4 h, peak at 48 – 72 h, persist for a month
- neutrophils – proteases, ROS, TNF-α , ILs

direct contribution or neuronal loss or an epiphenomenon?

- complement - MAC
- rodents: inhibition of complement activation attenuates perihematomal edema, concentrations of TNF- α, and inflammatory response
- TNF- α levels in patients correlate with degree of edema

# Mast cells and ICH: mediators



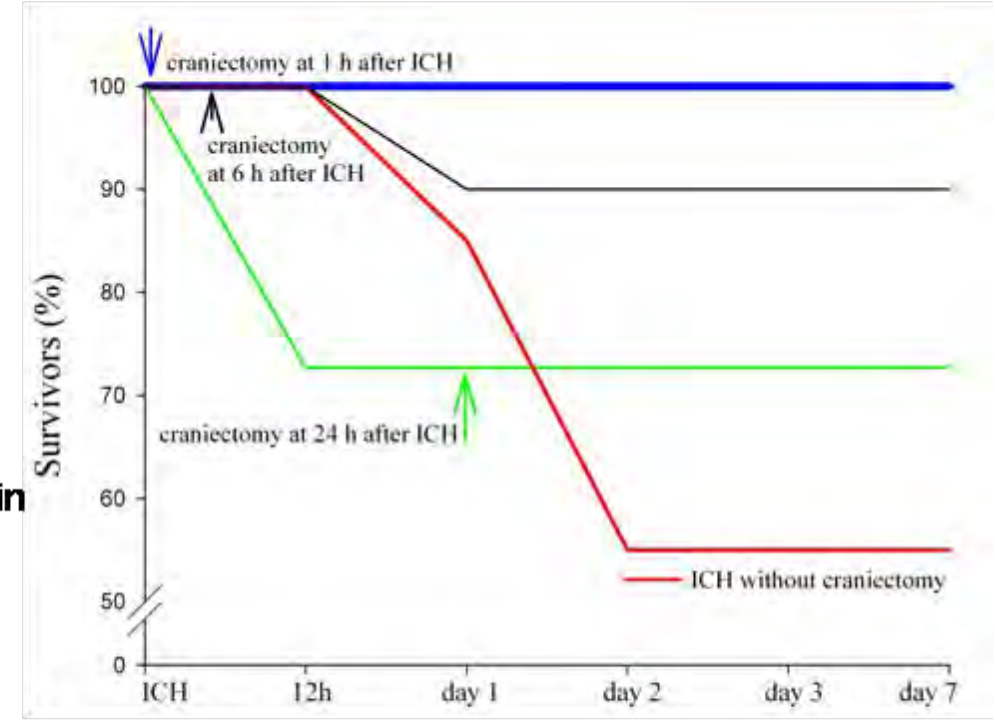
- vasoactive mediators
  - histamine, bradykinin, serotonin, leukotrienes
- proteolytic mediators
  - tryptase, chymase, cathepsins, gelatinases
- anticoagulant mediators
  - heparin
- tPA; fibrinolytic potential, (MC tumor in dogs)
- chemotactic mediators
  - eosinophil and neutrophil
  - platelet-activating factor
- cytokines
  - interleukins, TNF-α

# Conclusion: pathophysiology – therapeutic approaches

- **mass effect, ↑ ICP**
  - » » » **hematoma removal**
  - » » » **decompression**
- **hematoma growth, rebleeding**

**NO: aminocaproic and tranexamic acid, aprotinin**

- » » » **hemostasis (NovoSeven)**
- **clot-derived factors**
  - thrombin inhibitors: argatroban
  - thrombin preconditioning
- **hemoglobin breakdown products**




**iron chelators (deferoxamine)**

**ICH → RBCs lysis → Hb → Iron → ROS → Brain damage**

**HO inhibitors**

**heme oxygenases (HO)**

**antioxidants**