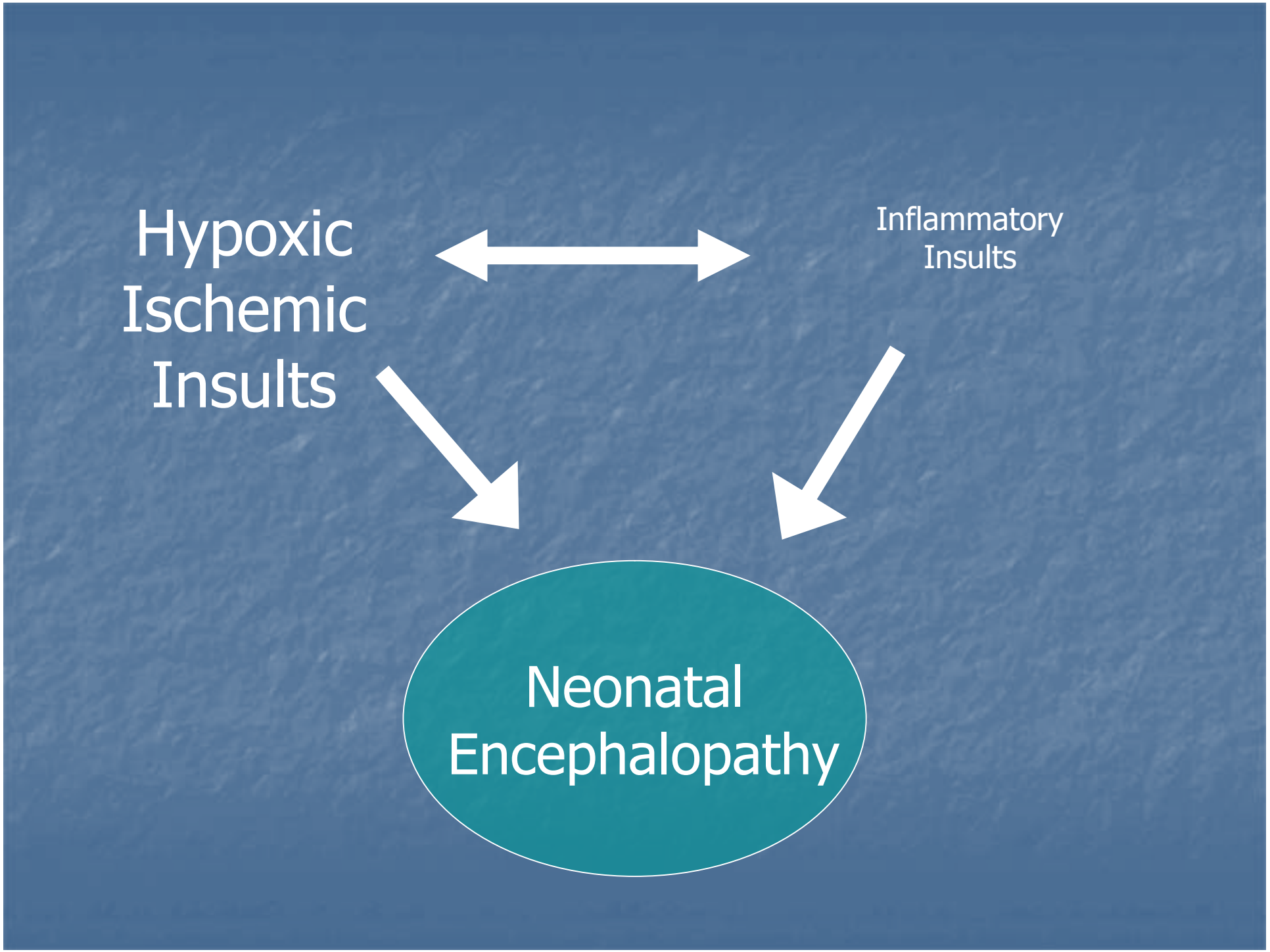
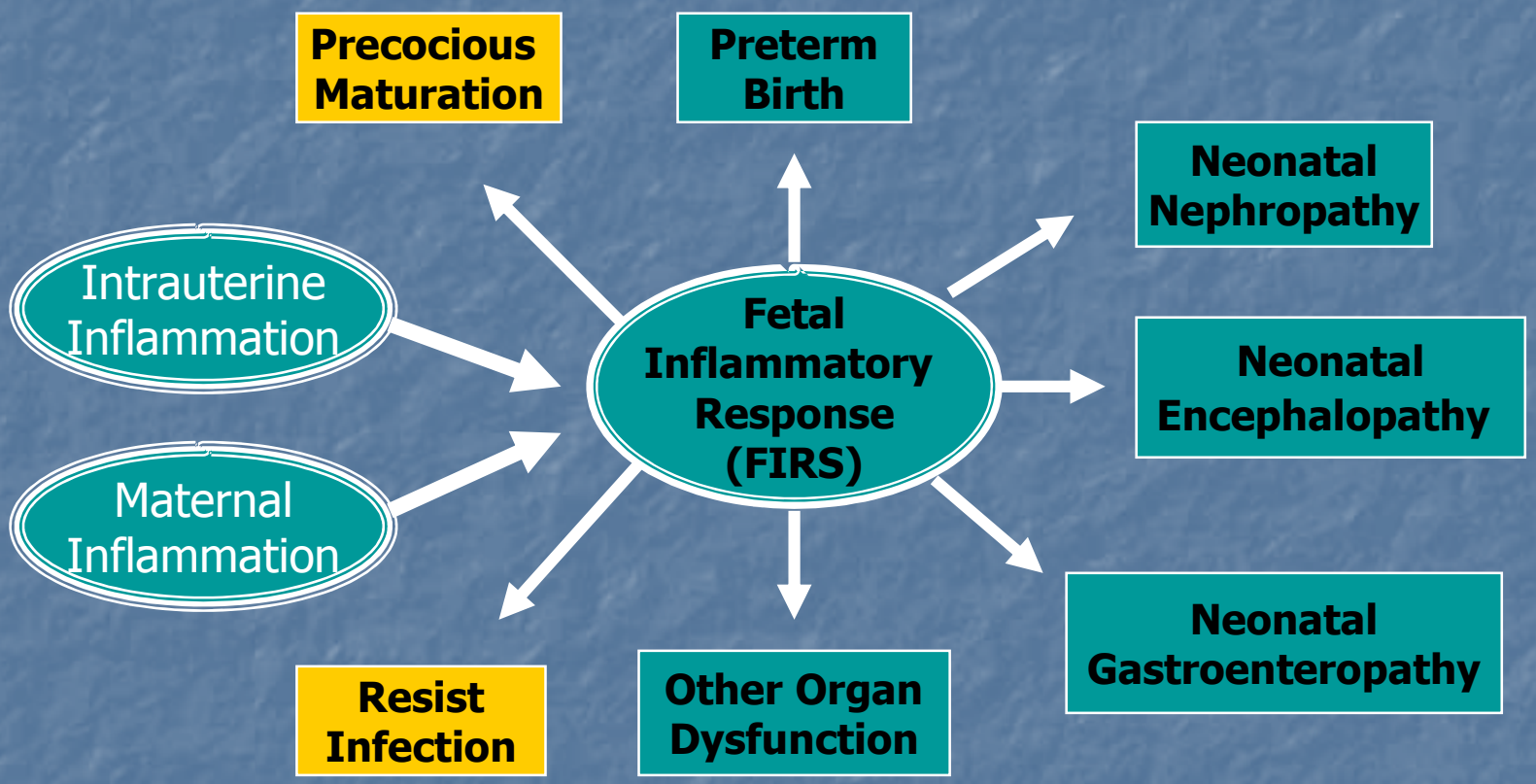
Neonatal Encephalopathy

Jon Palmer, VMD
New Bolton Center

Hypoxic Ischemic Encephalopathy
Neonatal Encephalopathy
Neonatal Encephalopathy Syndrome
(HIE)

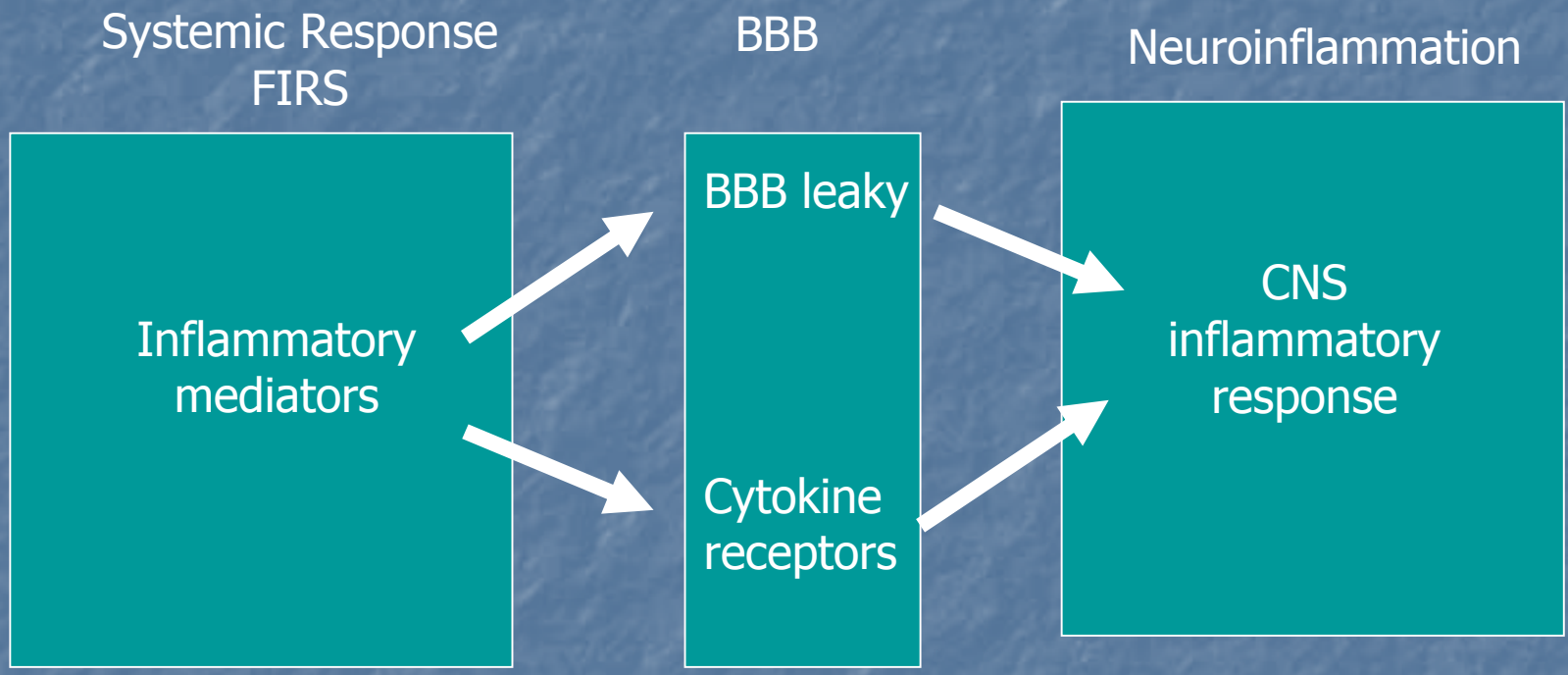

Hypoxic
Ischemic
Insults
Inflammatory
Insults
Neonatal
Encephalopathy


Precocious Maturation
Preterm Birth
Neonatal Nephropathy
Intrauterine Inflammation
Fetal Inflammatory Response (FIRS)
Neonatal Encephalopathy
Maternal Inflammation
Neonatal Gastroenteropathy
Resist Infection
Other Organ Dysfunction

Septic Encephalopathy

- Fetal
  - Neuroinflammation
  - FIRS (fetal inflammatory response syndrome)
    - Fetal placentitis
- Maternal
  - Maternal placentitis
  - SIRS
  - Focal maternal infections

Septic Encephalopathy



Preconditioning vs Sensitization

- Preconditioning
  - Exposure low levels of messengers
  - Protection
    - Repeat exposure to higher levels of mediators
    - Hypoxic ischemic insults
- Sensitization
  - Negative preconditioning
  - More susceptible
    - Repeat exposure of inflammatory messengers
    - Mild hypoxic ischemic insults

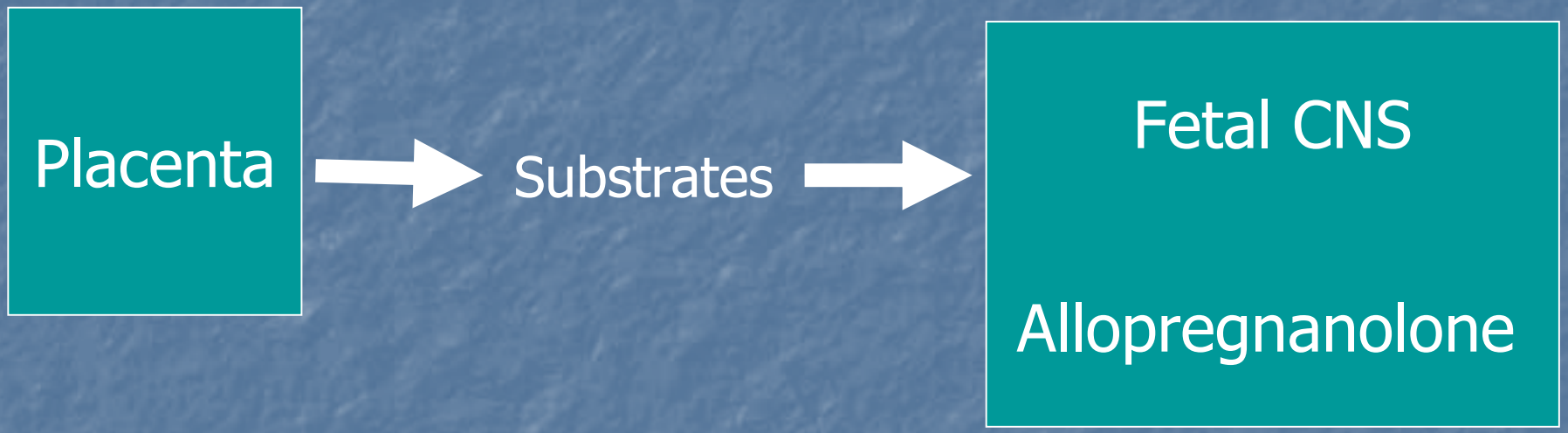
Neuroinflammation

- Important in the pathogenesis of
  - Septic encephalopathy
  - Hypoxic ischemic encephalopathy
- Microglia cells are key
  - Up-regulation of proinflammatory cytokines
  - Up-regulation of trophic factors
- Can result in
  - Morphological alterations
  - Biochemical alterations
  - Functional alterations

Neuroinflammation

- Response depends on mix
  - Proinflammatory
  - Anti-inflammatory
  - Specific mediators
- Mild disease – often no morphologic changes
  - Motor
  - Perceptual, visual
  - Behavioral
  - Cognition
  - Excitatory responses
- Excitotoxicity

Neurosteroids



- Protect the brain during fetal life
- Responsible for the somnolence
- At birth
  - Removal of the placental
  - Levels drop rapidly
  - Fetus to “awake up”

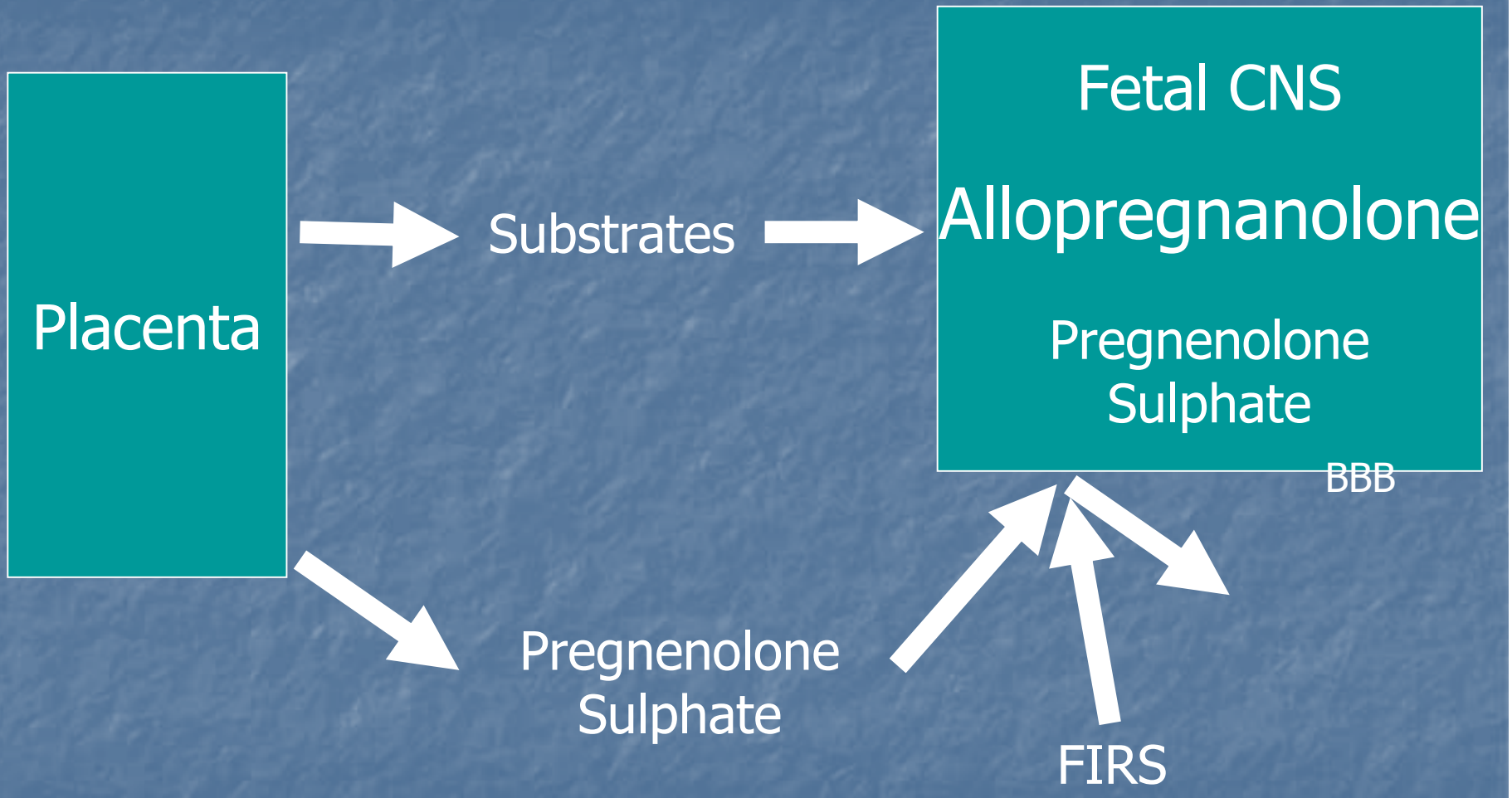
Neurosteroids

- Allopregnanolone
  - Brain levels induced by
    - Inflammatory mediators
    - Hypoxic ischemic insults
  - Protect against neuroexcitatory toxicity
  - Marked anti-seizure actions
  - Raise seizure threshold
  - Induces somnolence

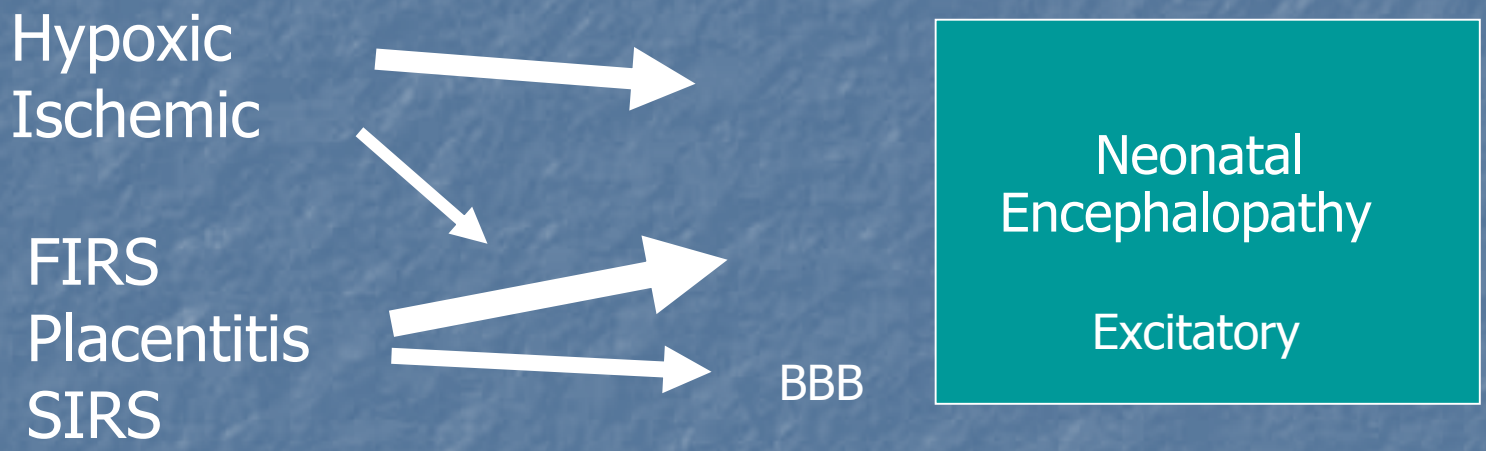
Neurosteroids

- Pregnenolone and pregnenolone sulphate
  - Placenta also secretes
  - Excitatory action in the brain
  - Cross the blood brain barrier
    - Normal – slow
    - Abnormal BBB – rapid transfer
    - Inflammation
    - Hypoxic ischemic insult

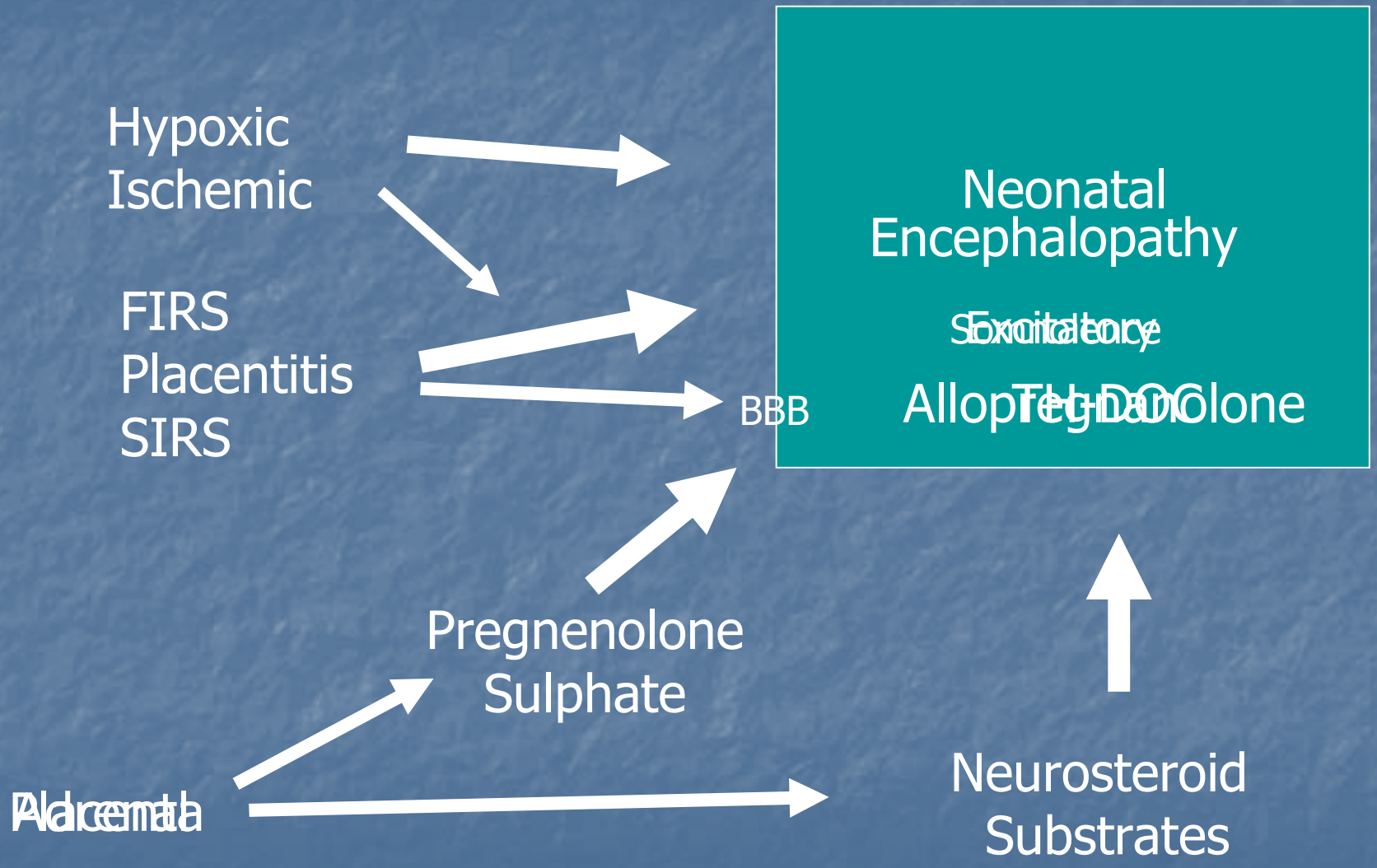
Neurosteroids



Neonatal Encephalopathy



Neonatal Encephalopathy



Typical Clinical Course

- Born near normal behavior
- Initial signs – excitatory
  - Constant activity –wandering, not lie down
  - Hyper-responsiveness
  - Hypertonus
  - Culminating in tonic-clonic seizure-like behavior
- Onset of somnolent phase
  - Stress induced adrenal steroidogenesis
  - Neuroinflammation induces neurosteroids
  - Healing period
- Recovery

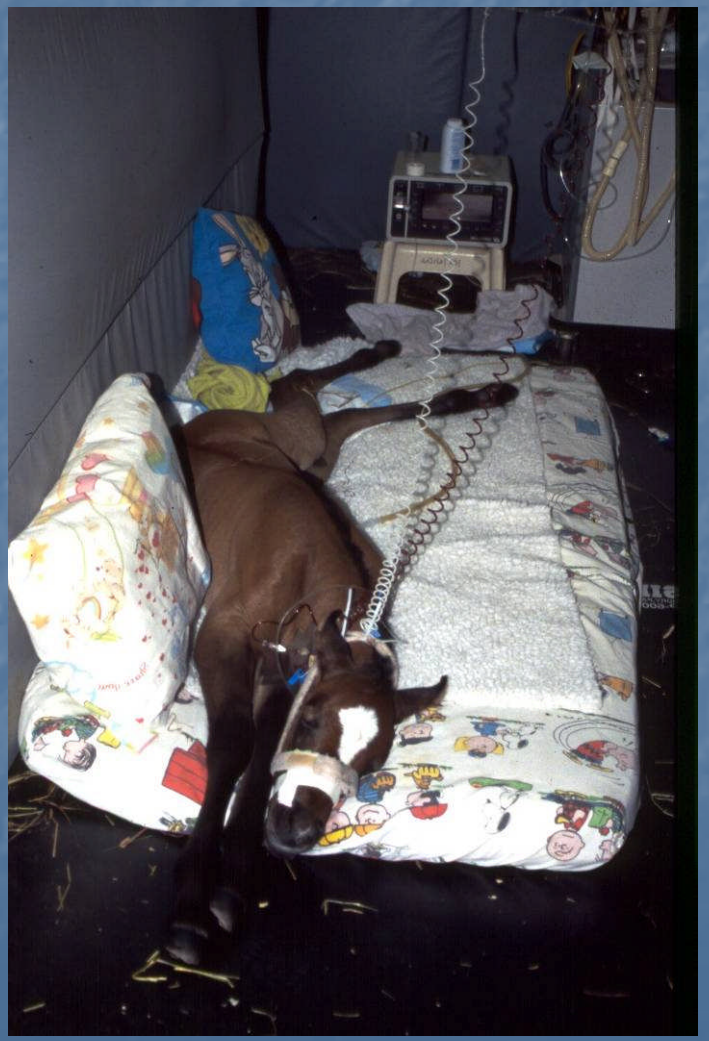
Typical Clinical Course

- Born seizure-like behavior
  - Less placental steroidogenesis
    - Lower levels protective neurosteroids
  - Inflammatory mediators
    - Induced blood brain barrier deficits
    - Allow sulfated neurosteroids into CNS
- With neonatal stress onset of somnolent phase
  - Stress induced adrenal steroidogenesis
  - Neuroinflammation induced CNS neurosteroids
  - Healing period
- Adrenal insufficiency
  - Less steroidogenesis
  - Less production of protective neurosteroids

Changes in responsiveness

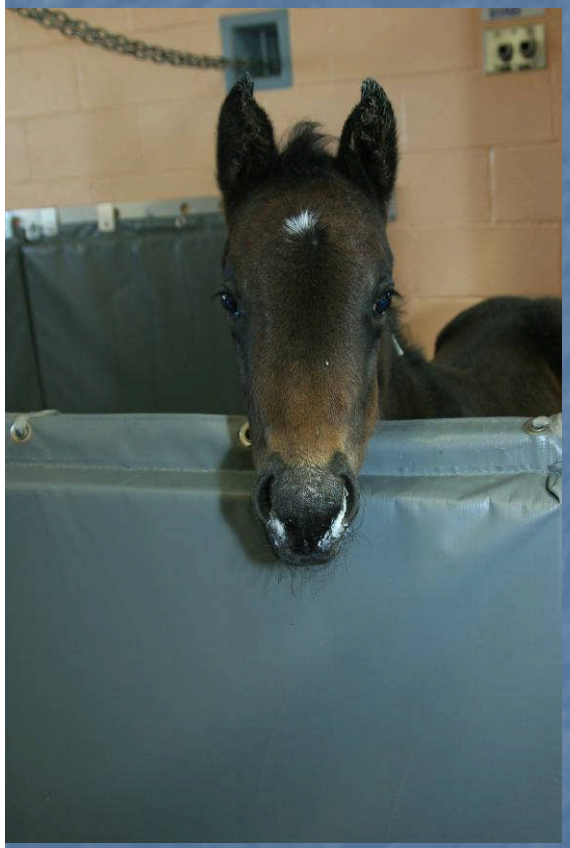
Changes in muscle tone

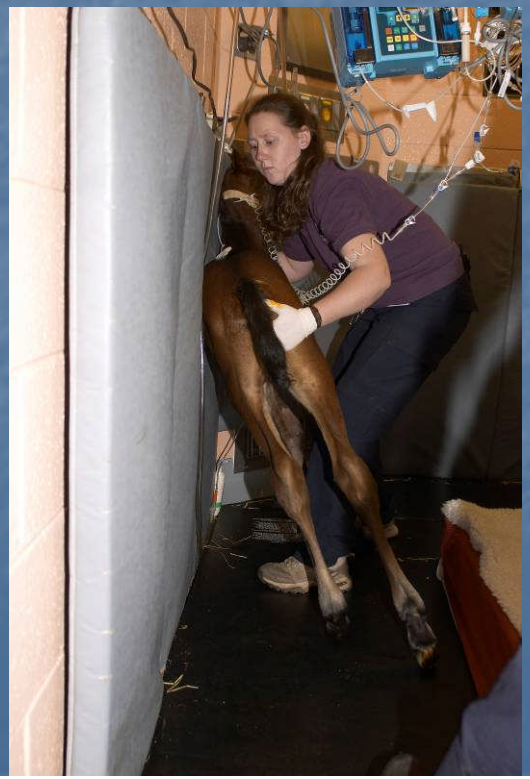
Changes in muscle tone



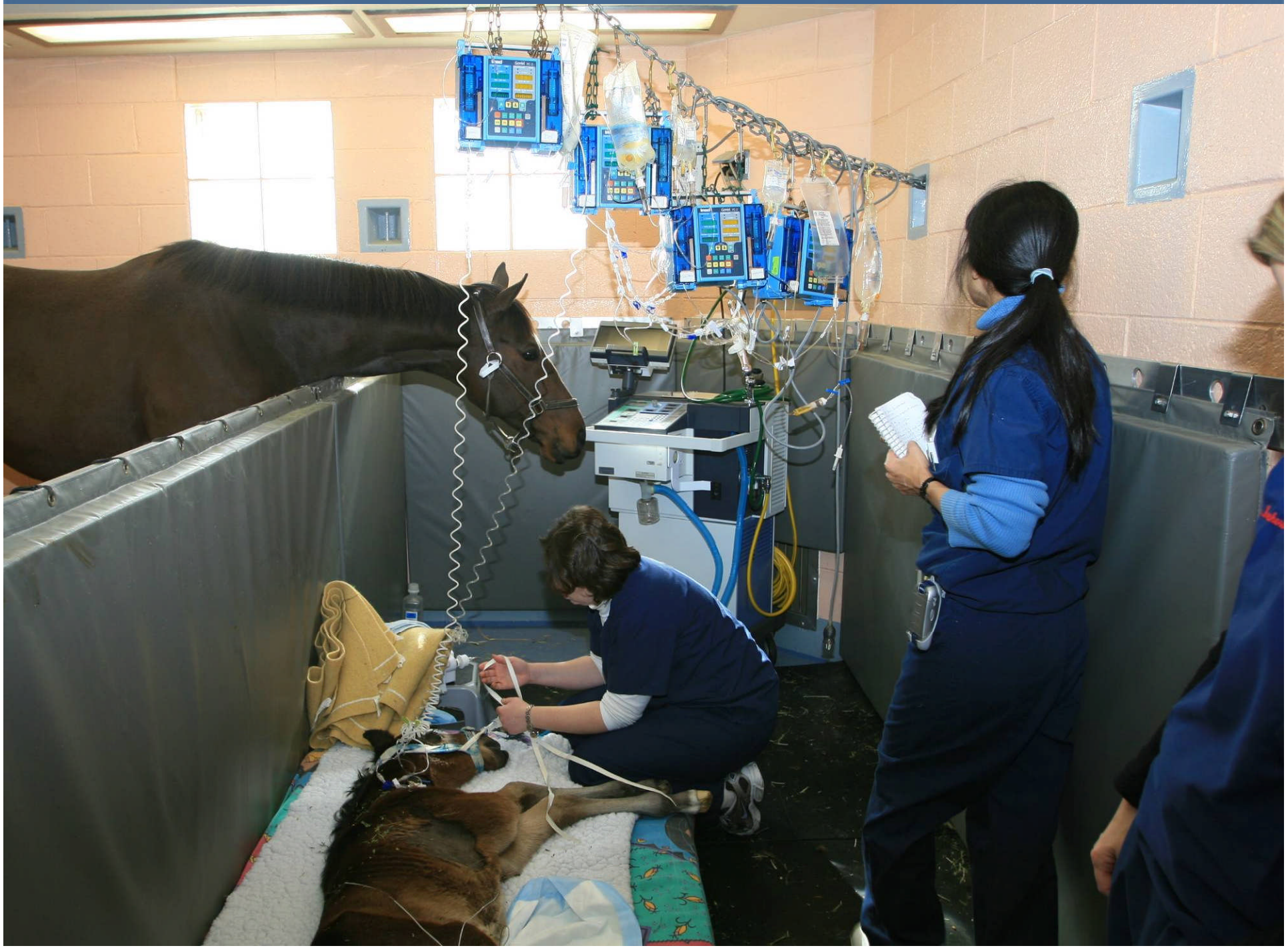
Changes in behavior

Brain stem damage





Seizure-like behavior



Therapy?

Evidence Based

Traditions

Beliefs

Experience Based

Therapy

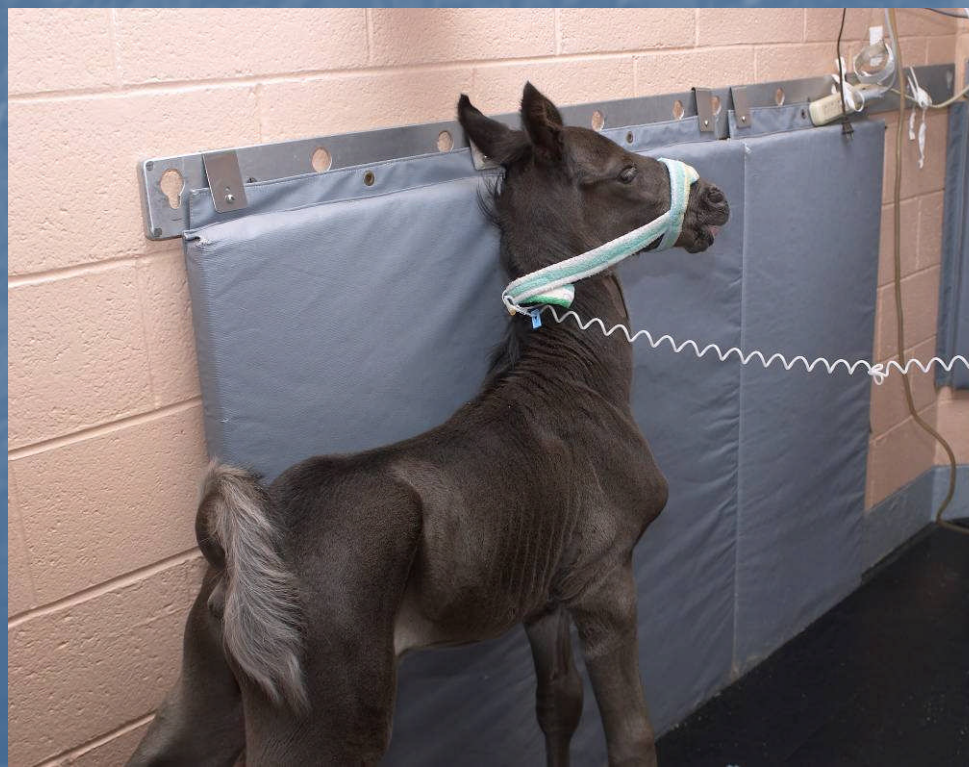
- Support cerebral perfusion
  - Insure volemia
    - Careful fluid replacement
  - Defend perfusion
    - Inopressor therapy
- Insure oxygen delivery
  - Achieve pulmonary O_2 loading
  - Avoid anemia
- Nutritional support
  - Permissive underfeeding

200 Cases of NE

- All treated with only supportive therapy
- 78% survived
- 22% nonsurvivros:
  - 7% died
  - 15% euthanised
- Failures: 44 cases
  - Sepsis – 24 cases
  - NE – 5 firm cases – 2.5%
    - Refractory shock – also septic – 7 more cases
    - 12 possible cases – 6%
  - NEC – 7 cases
  - Congenital defects – 4 cases
  - Renal failure , kernicterus, arrhythmia , cardiac tamponade

Therapy

- DMSO
- Mannitol
- Thiamine
- MgSO4
- Others



MgSO4

- Retrospective study preeclampsia
  - Lower risk NE
  - 7% of 42 VLBW newborns had CP after MgSO4
  - 36% had CP if not exposed to MgSO4
- Block Ca channels – rational

MgSO4

- Prospective studies
  - Preeclampsia protects
  - MagNet trial
    - Prenatal exposure MgSO4
    - Increase risk of death
      - X 10.7 times (95% CI 2.9–18.5%; P 0.02)
    - Decreased neonatal cerebral perfusion
  - Cord levels Mg correlate with neonatal death
  - Is it dose of MG
  - Is it SO4 and not Mg?
- Meta-analysis - Cochrane 2009
  - Antenatal Rx in VLBW (premature)
  - Need to treat 63 pregnant women to benefit 1 child

Seizure Control

Phenobarbital? Midazolam? Others?

Seizure Control

- Phenobarbital
- Midazolam
  - Apoptosis - immature neurons
  - Adverse effects – 16% neonates
    - Increased IVH, periventricular leukomalacia
    - Transient abnormal neurologic movement
      - Seizures
      - hypertonia or hypotonia
      - myoclonus
      - Extrapyramidal movements
        - Chorea
        - Dyskinesia
    - Longer hospital stay
    - Increased mortality

Pead & Child Health 33:335-8, 1997; *Anesthesi 87:1106-17, 1997;* J Neuro Anesth 5(4):232-6, 1993; *Anesthes 87(5):1106-17, 1997;* Proc Nat Sci Council, Rep of China - Part B, Life Sciences. 12(3):174-9, 1988

Seizure Control

- Midazolam
  - Cerebral Blood Flow
    - Decrease 12% at 5 min; decrease 30%
    - Changes in discrete brain regions
      - Dose-related
    - Decreases blood flow velocity
- Ketamine
  - Intracranial Hypertension
    - Primarily in the face of hypercapnea
  - Anesthetic-induced Neurotoxicity
    - Pathological vacuolation of neurons
    - Apoptosis - immature neurons

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primum non nocere