

### Viewing Time

The program will take up to one hour to complete.

### Target Audience

This program is designed for primary care physicians.

Other health care professionals working with patients and their families may also find this program of interest.

### Faculty Disclosure

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### Faculty Disclosure

**Raghu Rao, MD**, has disclosed no actual or potential conflict of interest in relation to this educational activity.

During this educational activity **Dr. Rao** will not be discussing the use of any commercial or investigational product not approved for any purpose by the FDA.

### Neonatal Hypoglycemia

**Raghu Rao, MD**

Pediatric Neonatology, University of Minnesota,  
Minneapolis, Minnesota

### Neonatal Hypoglycemia

*A lecture about the diagnosis and treatment of hypoglycemia in newborn infants.*

### Program Objectives

*Upon completion of this program, participants should be able to:*

- Understand the etiopathogenesis of hypoglycemia and hypoglycemia-associated brain injury in newborn infants
- Recognize the issues related to diagnosis and treatment of neonatal hypoglycemia
- Manage neonatal hypoglycemia based on operational thresholds of plasma glucose values

### Disclaimer

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### Receiving CME Credit

To receive CME credit you must view the entire program and complete the evaluation form at the end.

## Neonatal Hypoglycemia

Raghavendra Rao, MD

Division of Neonatology, Department of Pediatrics  
Center for Neurobehavioral Development  
University of Minnesota

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## Neonatal Hypoglycemia

- Most common in neonates
- Potential risk of CNS injury
- Presenting feature of inborn endocrine/metabolic disorders
- Controversy re. definition, significance and management

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**“Malpractice verdict tops \$18 million”**

“\_\_\_\_\_ Hospital and two local pediatricians are responsible for an 8-year-old boy’s permanent brain damage, according to 12 jurors who awarded the boy and his mother more than \$18 million, the highest judgment ever in \_\_\_\_\_ County. \_\_\_\_\_ Hospital was found 70 percent responsible for \_\_\_\_\_’s condition and each pediatrician, 15 percent. “We felt the brain damage occurred because of the hypoglycemia,” said \_\_\_\_\_ of \_\_\_\_\_. \_\_\_\_\_ Hospital and its staff did not follow the proper procedures. That was the most substantial factor in our decision.”

“Various experts testified that the child should have been watched more carefully because he was susceptible to hypoglycemia because of a condition his mother had while pregnant. Instead, they testified the child received no nourishment during his first three days because he would not nurse. According to medical records, \_\_\_\_\_’s blood sugar level was zero when a test was finally taken three days after his birth. Shortly afterward, he suffered a seizure and was taken to \_\_\_\_\_ Hospital in \_\_\_\_\_.”

“\_\_\_\_\_ said she didn’t think about filing a lawsuit until a few years after \_\_\_\_\_’s birth, when doctors would not answer questions she had regarding his brain damage”

(Source: <http://www.fansoffieger.com>; edited excerpt)

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(Source: <http://www.fansoffieger.com>; edited excerpt)

**TABLE 1 Most Prevalent Conditions Resulting in Malpractice Lawsuits (in Order of Frequency)**

| Condition                               | Average Indemnity (for All Claims), \$ |
|---|--|
| 1. Brain-damaged infant                 | 440 379                                |
| 2. Meningitis                           | 437 423                                |
| 3. Routine infant or child health check | 155 039                                |
| 4. Respiratory problems in newborns     | 270 607                                |
| 5. Appendicitis                         | 116 285                                |
| 6. Pneumonia                            | 239 531                                |
| 7. Specified nonteratogenic anomalies   | 186 708                                |
| 8. Premature birth                      | 250 031                                |
| 9. Birth                                | 286 407                                |
| 10. Asthma                              | 193 414                                |

McAbee et al., *Pediatr* 2008



**Overview**

- Perinatal metabolic adaptation
- Populations at risk for hypoglycemia
- Hypoglycemia and the developing brain
- Diagnosis and treatment considerations

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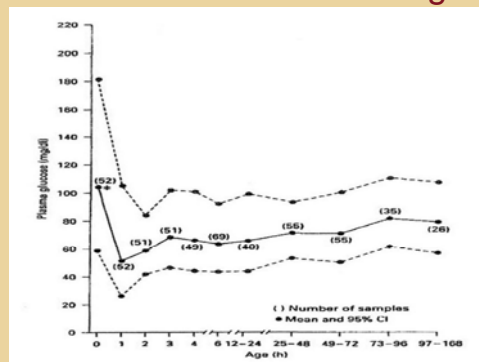
**Perinatal Glucose Metabolism**

- Fetal glucose metabolism
  - Dependent on supply from mother
  - Minimal endogenous production
- Cord glucose: 60-80% of maternal glucose
- Fetal to neonatal transition
  - From high carbohydrate/low fat to low carbohydrate/high fat substrate mix
  - From continuous supply to intermittent periods of feeding and fasting

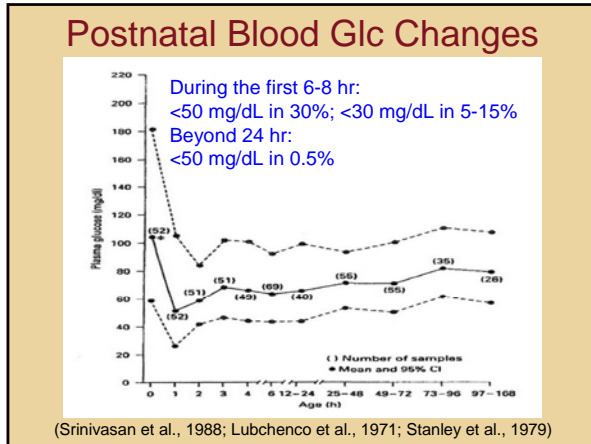
(Marconi et al., 1996)



**Postnatal Blood Glc Changes**



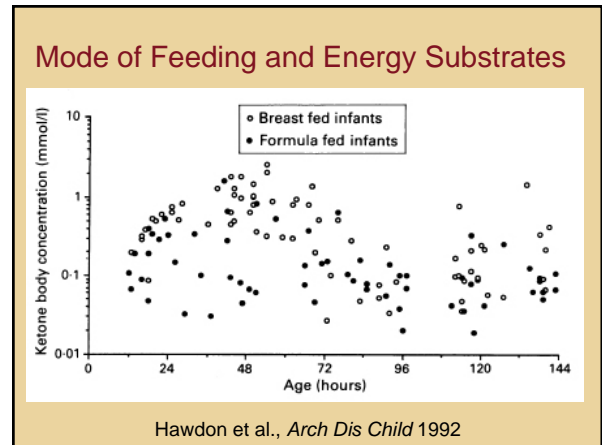
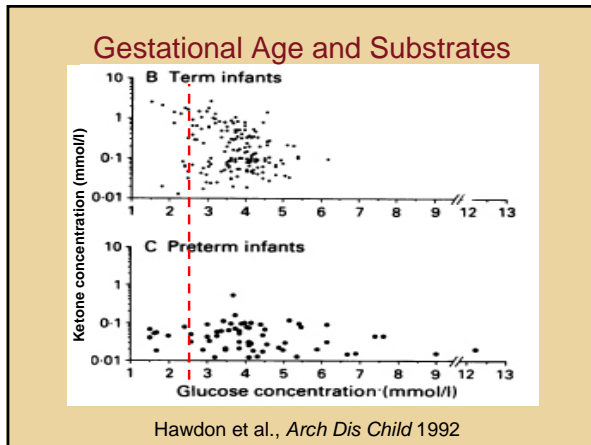
(Srinivasan et al., 1988)



### Metabolic Adaptation During Fasting

- Glycogenolysis
  - Hepatic glc release: 4-6 mg/kg per min
- Gluconeogenesis
- Adipose tissue lipolysis
- Fatty acid oxidation and ketogenesis
- Hormonal and enzymatic regulation

Stanley & Caplin, 2008



### Classification of Neonatal HG

- Transient hypoglycemia
  - During the first 12-24 hr of life
- Persistent hypoglycemia
  - Persistent hyperinsulinemia
  - Counterregulatory hormone deficiencies
  - Inborn errors of carbohydrate and fatty acid metabolism

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### Transient Neonatal HG

- Developmental lags in gluconeogenesis and ketogenesis ± poor hepatic glycogen stores
  - Normal developmental lag, prematurity, SGA
- Transient hyperinsulinism
  - Infants of diabetic mothers
  - Perinatal stress (e.g. SGA, HIE, PIH)
  - Other conditions (e.g. Rh isoimmunization, Beckwith Wiedeman syndrome)

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## Hypoglycemia and the Developing Brain

- Glucose is the principal substrate
- Capable of using non-glucose substrates
  - Ketone bodies, lactate, amino acids
- Additional adaptive mechanisms
  - Increased CBF, brain glycogen

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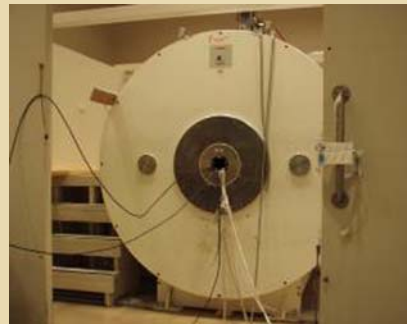
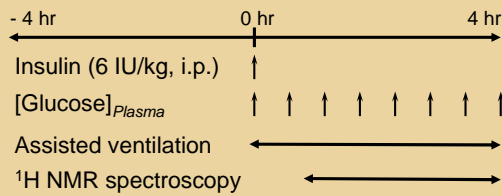
## Neurochemical Changes in the Developing Rat Hippocampus During Acute Hypoglycemia

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## Methods

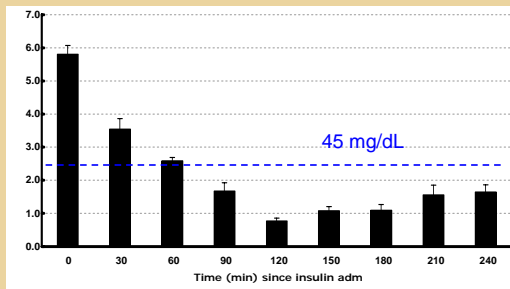
14-day-old Sprague-Dawley rats (35 gm)



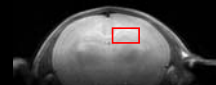
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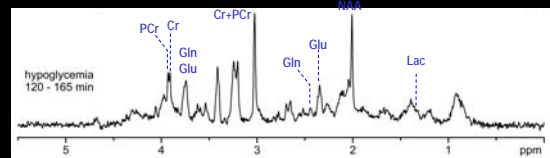
## Plasma Glucose Concentration



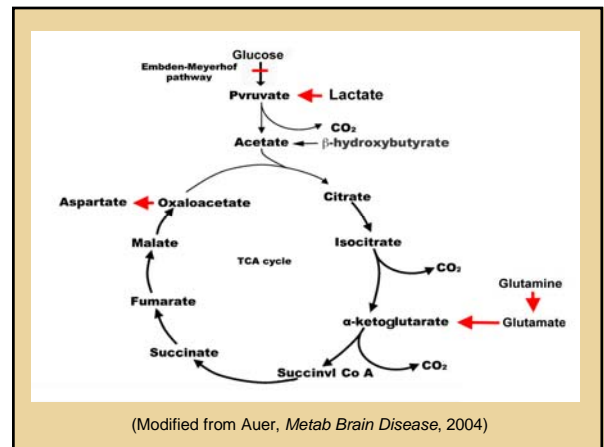
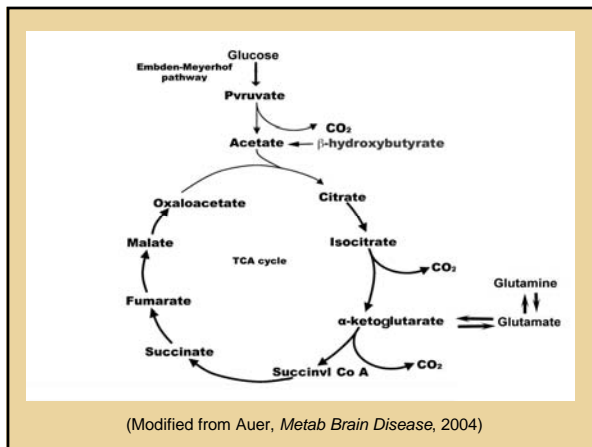
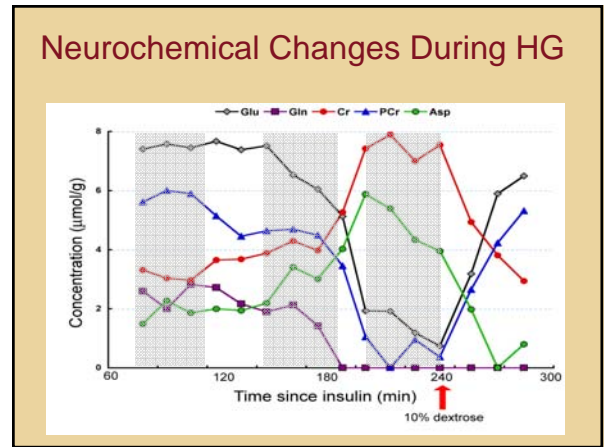
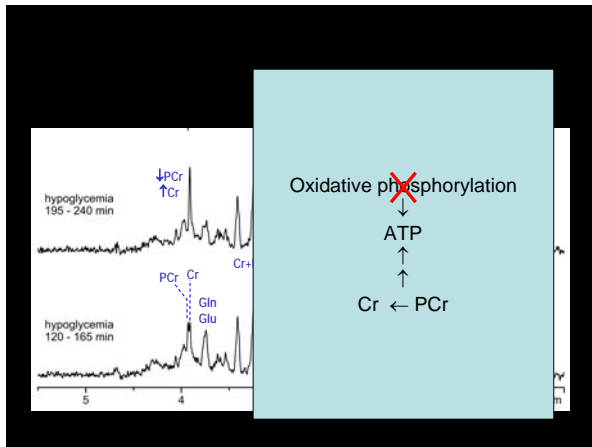
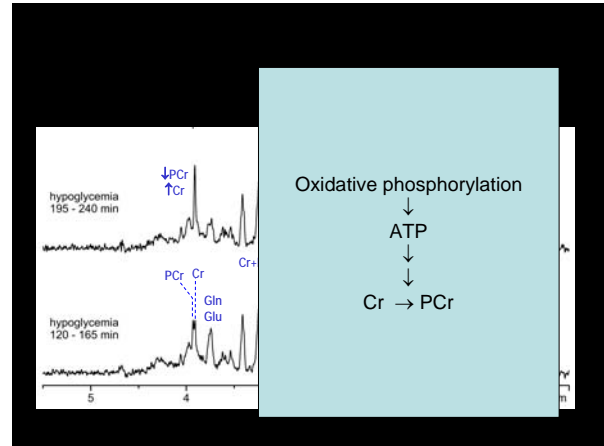
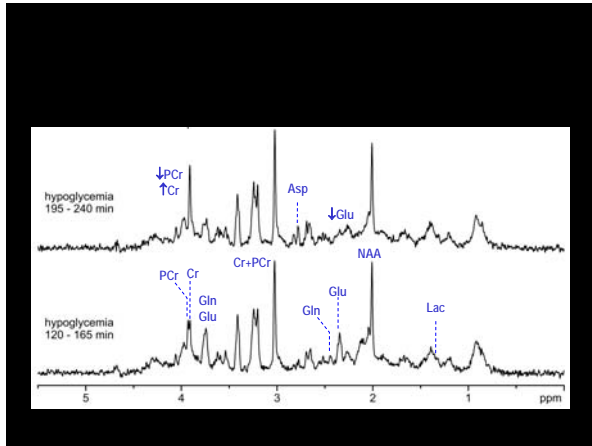
(Mean±SEM, n=7-11 at each time point; P<0.001, ANOVA )

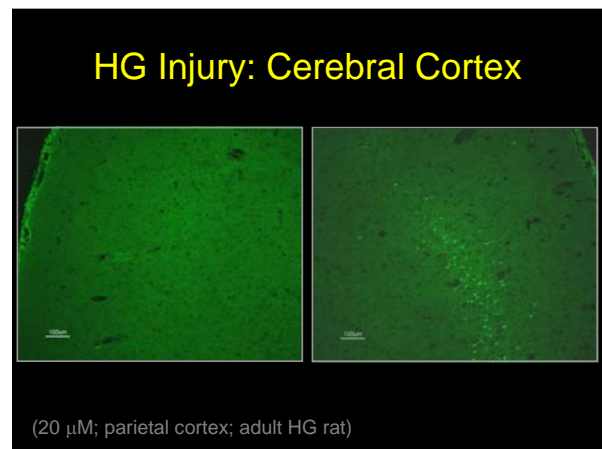
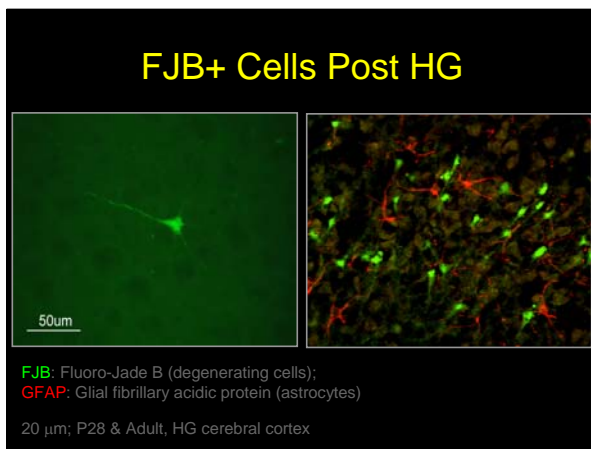
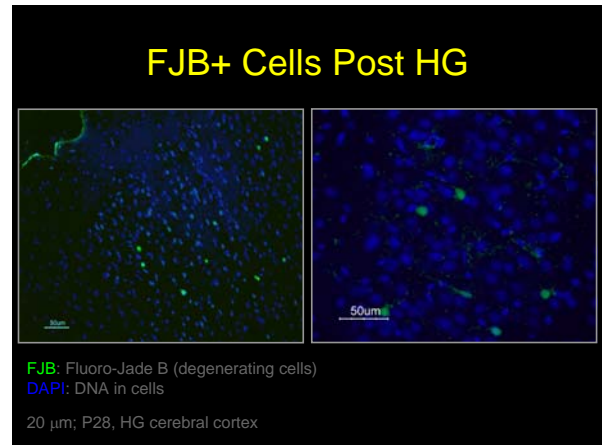
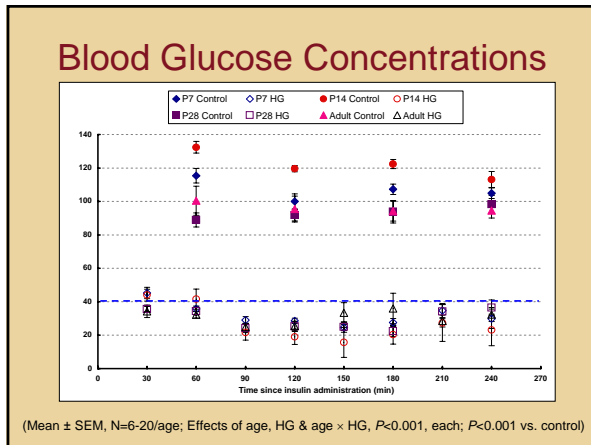
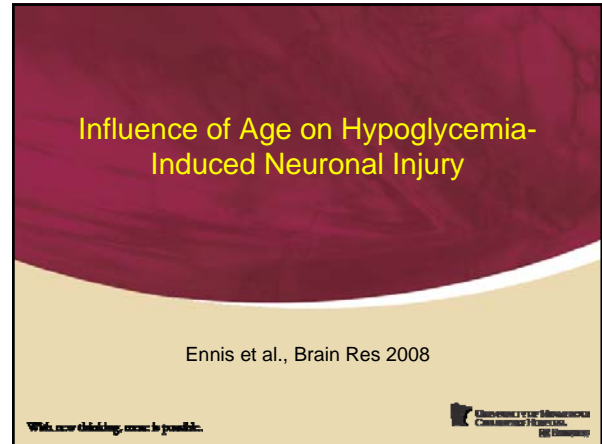
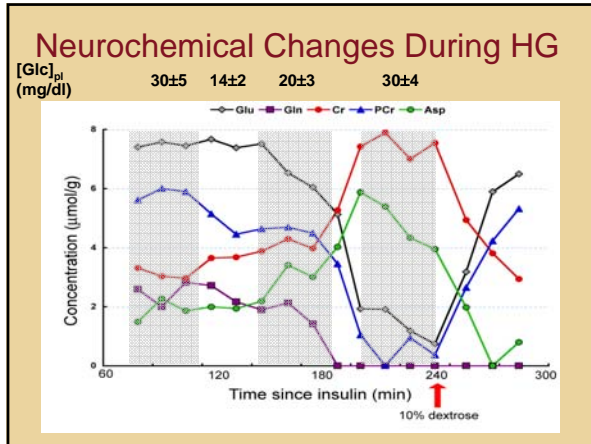


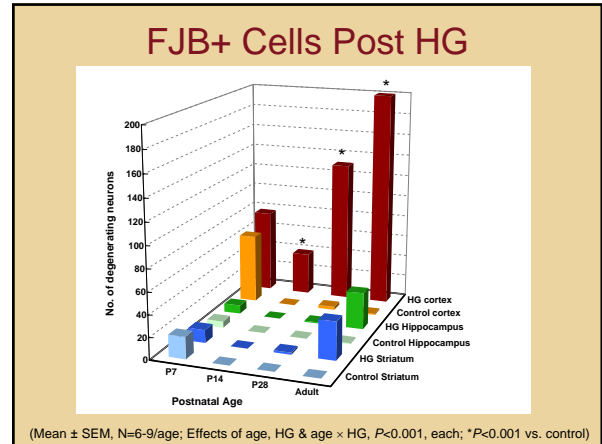
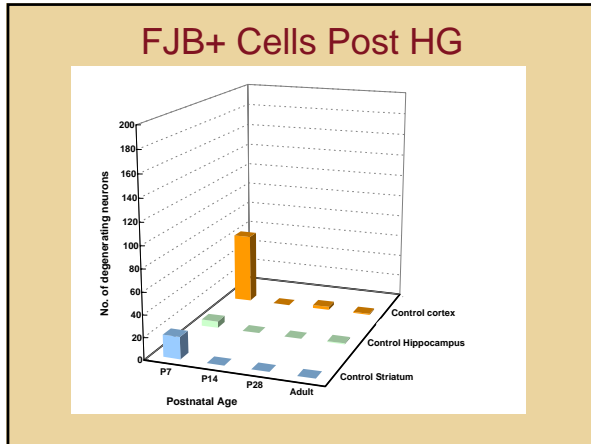
Volume of interest (2.3×1.5×3.0 mm<sup>3</sup>)



# Raghu Rao, MD Neonatal Hypoglycemia





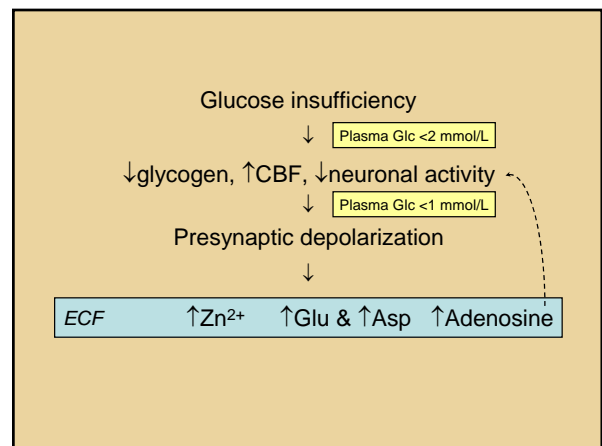


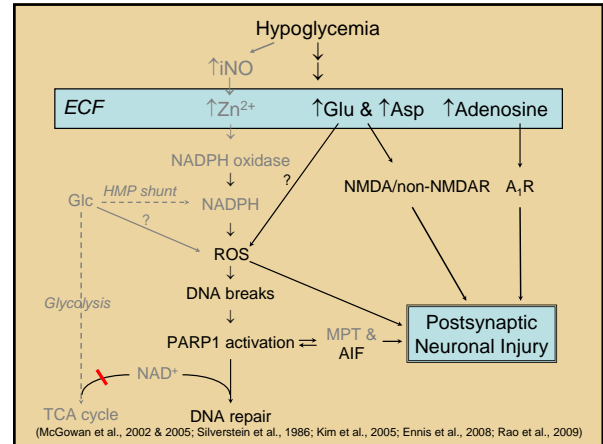
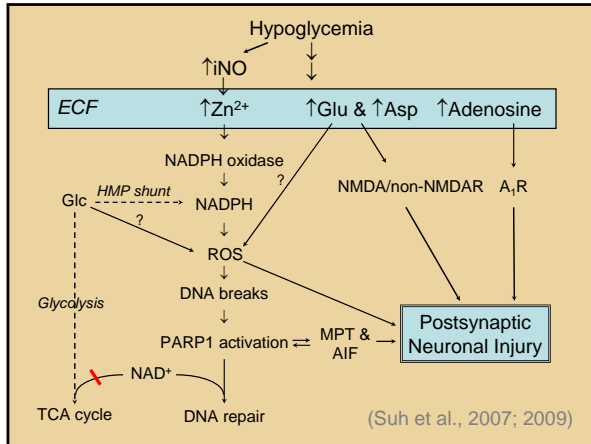
- ### Age-Related Regional Variations
- Developing rats
    - Cingulate, orbital, temporal & parietal
  - Adult rats
    - Temporal, parietal & piriform
    - Hippocampus & striatum
  - Hypothalamus spared at all ages
- With new thinking, more is possible. University of Wisconsin - Madison Children's Hospital. E. Hershner

- ### Potential Reasons for Age-Related Regional Specificity
- Presence of active neurons & synaptogenesis
  - Loss of autoregulation
  - Glucose needs/stores
  - Ability to use non-glucose substrates
  - Concentration of insulin receptors
  - Genomic responses
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### Pathogenesis of Neuronal Injury in Hypoglycemia

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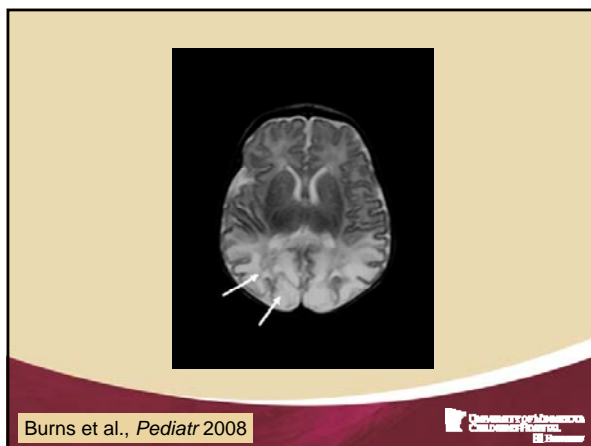


## Hypoglycemia-associated Brain Injury in Human Neonates

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- ## Hypoglycemia and Brain Injury
- Over 50 studies since 1959
  - Motor and cognitive impairments
  - Extensive neuronal and glial injury
  - Gray and white matter injury on MRI
    - Predilection for occipital region
- Boluyt et al., 2006; Anderson et al., 1967; Burns et al., 2008



- ## Other Neurological Sequelae
- Neurobehavioral Deficits
    - Deficits in attention
    - Deficits in memory and perception
    - Decreased arithmetic score
  - Seizures-complex partial
  - Minor motor deficits
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## Predicting the Risk of CNS injury in Neonatal Hypoglycemia

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No universally accepted level or duration that is associated with the risk of CNS injury


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### How Low Can I Go? The Impact of Hypoglycemia on the Immature Brain

For the clinician, the experimental and human clinical data are clear that hypoglycemia (blood glucose level < 45 mg/dL), isolated or combined with mild hypoxia-ischemia, is injurious to the newborn brain and must be monitored for closely and managed aggressively to avoid adverse consequences. The study by Burns et al<sup>1</sup> also

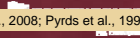
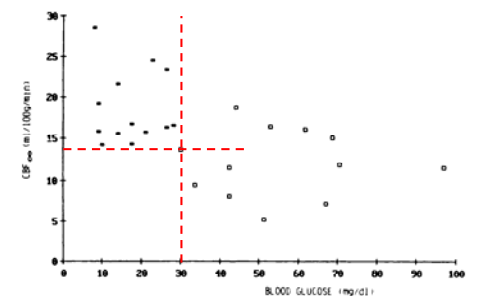
Inder, *Pediatr* 2008



### Plasma Glucose Values and Risk of CNS Injury


- Plasma glucose < 47 mg/dL
  - Abnormal ABR
  - Ventriculomegaly/PVL
  - Cognitive deficits at 18-60 months
- Increased CBF with BG < 30 mg/dL

Koh et al., 1988; Lucas et al., 1988; Duvanel et al., 1999; Beardsall et al., 2008; Pyrds et al., 1990

**Fig 1.** Cerebral blood flow (CBF<sub>sc</sub>) vs blood glucose values in 25 preterm neonates 2 hours after birth. ■, blood glucose <30 mg/dL; □, blood glucose ≥30 mg/dL.

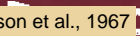
Pyrds et al., *Pediatr Res* 1990

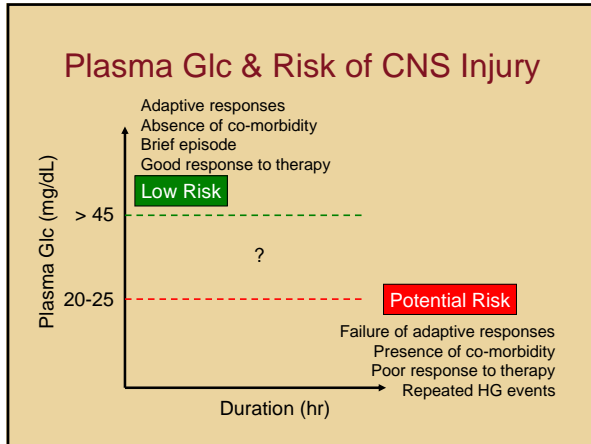


### Plasma Glucose Values and Risk of CNS Injury

- Increased risk at plasma glucose <20-25 mg/dL
  - White matter injury in 94%
  - Extensive neuronal and glial injury
- Most had seizures

Alkalay et al., 2006; Burns et al., 2008; Anderson et al., 1967





### Risk of Brain Injury in HG

- Associated with severe, recurrent or prolonged hypoglycemia
  - Failure of adaptive mechanisms
  - Presence of co-morbidities (seizures, hypoxia-ischemia, sepsis)
- Potential risk with recurrent “moderate” hypoglycemia in preterm and SGA infants

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## Management of Neonatal Hypoglycemia

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<http://www.wiley.com>

### Definition of Neonatal Hypoglycemia: Plasma Glucose

- Without regard to clinical signs
  - A value 2 SD below ‘normoglycemia’
- A value associated with
  - Clinical signs (*Whipple’s triad*)
  - Neurophysiological changes
  - Neuropathological changes

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### Diagnosis Based on Plasma Glucose

- Advantages:
  - Practical
  - Association with CNS effects
- Disadvantages:
  - No universal definition (18-70 mg/dL)
  - May represent normal homeostasis
  - May not reflect the role of other substrates
  - Dependent on screening methods

Koh et al, 1997

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### Diagnosis Based on Presence of Clinical Signs

- General Signs
  - Temp instability
  - Poor feeding
  - Diaphoresis
- Cardio-pulmonary Signs
  - Apnea/tachypnea
  - Cyanosis/pallor
- CNS signs
  - High-pitched cry
  - Lethargy
  - Hypotonia
  - Irritability
  - Tremors
  - Seizures
  - Coma

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### Diagnosis Based on Presence of Clinical Signs

- General Signs
    - Temp instability
    - Poor feeding
    - Diaphoresis
  - Cardio-pulmonary Signs
    - Apnea/tachypnea
    - Cyanosis/pallor
    - Bradycardia
  - CNS signs
    - High-pitched cry
    - Lethargy
    - Hypotonia
    - Irritability
    - Tremors
    - Seizures
    - Coma
- Most are non-specific  
• No correlation with long-term sequelae

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### Symptomatic Vs. Asymptomatic Hypoglycemia

- Greater risk of neurological sequelae with symptomatic hypoglycemia
  - 35-50% Vs. 16-20% for asymptomatic
  - Presence of seizures increases the risk
- Problems
  - Categorical classification of a likely continuous variable
  - Asymptomatic HG due to failure of counter-regulation

(Williams 1997; Singh et al., 1990; Cornblath et al., 2000)

### Management Considerations

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### Management Goals

- Prevention of hypoglycemia and its complications
- Detection of the condition without over- or under-diagnosis
  - Criteria for screening
  - Methods used for screening
- Optimal treatment without hindering
  - Breastfeeding and mother-infant bonding
  - Normal postnatal homeostasis

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### Management: Approach

- Detailed history
  - Antenatal, intranatal and postnatal
- Clinical examination
  - GA, size for GA, hepatomegaly, midline defects, prolonged jaundice, microphallus
  - Clinical signs attributable to HG
- Blood glucose levels
  - Cot-side screening with lab confirmation
  - Symptomatic or at-risk infants

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## At-Risk Populations

### Maternal/Fetal Conditions

Intrapartum glc infusion  
Diabetes mellitus  
Drugs:  $\beta$  blockers, oral hypoglycemic agents  
IUGR  
Rh-isoimmunization  
Prematurity

### Neonatal Conditions

Failure to adapt  
Hypoxia-ischemia  
Infection  
Hypothermia  
Hyperviscosity  
Iatrogenic  
Cong heart disease  
PPHI, IEM, endocrine disorders

Cornblath et al., 2000



## Screening of At-Risk Populations

- Advantages: Early detection allows prompt treatment
- Disadvantages:
  - Lack of population-specific norms
  - Risk of over/under treatment
  - Cost (emotional, financial)
  - Lack of reliable and cheap screening tools

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## Precision of Screening Methods

- Sample-related
  - Arterial vs. venous vs. capillary
  - Alcohol contamination ( $\uparrow$ )
  - Polycythemia, storage at room temp ( $\downarrow$ )
  - Bilirubin, hemolysis and uric acid ( $\downarrow$ )
- Paper strip-related
  - Accuracy  $\pm 9$  mg/dL
  - Unreliable at very low plasma glucose levels
- Continuous vs. intermittent monitoring

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## Considerations During Treatment of Hypoglycemia

- Blood/plasma glucose
  - Absolute value
  - Trend over time
  - Response to feeding
- Presence of absence of clinical signs

(Rozance & Hay, 2006)



## Operational Thresholds of Plasma Glucose for HG

- Consider intervention if plasma glc  $< 45$  mg/dL and symptoms of HG
- $< 36$  mg/dL and presence of risk factors
- $< 60$  mg/dL in a neonate with PPHI
- Same criteria for term and preterm

Cornblath et al., 2000; AAP Pediatric Nutrition Handbook, 2009

## I. Symptomatic Infants

- Plasma Glc 35-45 mg/dL
  - Breastfeeding/formula/5% dextrose
  - IV glucose 4-6 mg/kg/min
- Plasma Glc 24-34 mg/dL
  - IV glucose 6-8 mg/kg/min
  - Attempt oral feeding as able
  - Consider other pathologies
  - Monitor glucose and observe closely

Cornblath et al., 2000; AAP Pediatric Nutrition Handbook, 2009

## II. Asymptomatic Infants

- Healthy full-term infants
  - Do not need screening and monitoring
  - Promote exclusive breastfeeding
- Infants with risk factors
  - Glc monitoring within 2-3 hr of life, before feeding or when symptomatic
  - Close observation and frequent monitoring if <36 mg/dL
  - Intervene if fails to improve or infant becomes symptomatic

Cornblath et al., 2000; AAP Pediatric Nutrition Handbook, 2009

## III. Infants with Glc < 25 mg/dL

- Intravenous glucose 200 mg/kg as 10% dextrose and GIR at 6-8 mg/kg/min
- Adjust GIR based on glc q 30 min
  - Therapeutic goal: >45-50 mg/dL
- Additional work up and adjuvant therapies for persistent hypoglycemia

Cornblath et al., 2000; AAP Pediatric Nutrition Handbook, 2009

## Neonate with Persistent Hypoglycemia

- Additional work-up if hypoglycemia persists
  - Beyond 24-48 hr of age
  - GIR >15 mg/kg/min
  - After use of steroids
- Consider congenital hyperinsulinemia
  - Insulin  $\geq 2$   $\mu$ U/mL when blood glc  $\leq 50$  mg/dL
  - Hypoketonemia (<2 mmol/L)
  - Low free fatty acids (<1.5 mmol/L)
  - Exaggerated response to glucagon (>30 mg/dL)
- Similar results in counterregulatory hormone deficiencies

Stanley & Caplin, 2008



## Adjuvant Therapies for HG

- Corticosteroids
- Glucagon
- Additional therapies
  - Diazoxide, chlorothiazide, nifedepine, octreotide
- Transfer to a specialty hospital
  - Near total pancreatectomy

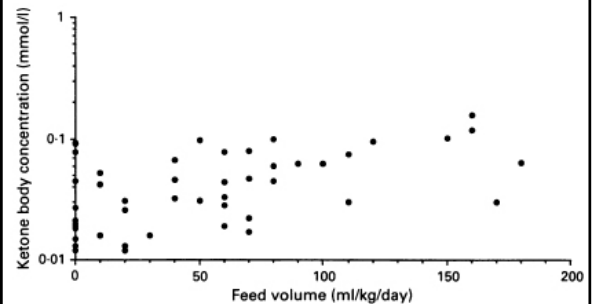
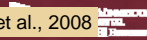
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## Other Considerations

- Total parenteral nutrition
  - Goal plasma glc >45-50 mg/dL
  - Addition of intralipids
- Infants on insulin infusion: 100-150 mg/dL
- Consider higher plasma glc in those with increased demand
- Attempt enteral nutrition in preterm infants

Sabel et al., 1982; Mitanchez, 2007; Beardsall et al., 2008



Hawdon et al., Arch Dis Child, 1991



### Unknown Issues with Treatment

- Suppression of “fasting” ketogenesis with parenteral glucose/nutrition
- Early introduction of formula milk on physiological homeostasis
- Risk of exaggeration of injury with glucose reperfusion

With new thinking, more is possible.



### “Malpractice verdict tops \$18 million”

“\_\_\_\_\_ Hospital and two local pediatricians are responsible for an 8-year-old boy's permanent brain damage, according to 12 jurors who awarded the boy and his mother more than \$18 million, the highest judgment ever in \_\_\_\_\_ County. \_\_\_\_\_ Hospital was found 70 percent responsible for \_\_\_\_\_'s condition and each pediatrician, 15 percent. **“We felt the brain damage occurred because of the hypoglycemia,”** said \_\_\_\_\_, of \_\_\_\_\_. \_\_\_\_\_ **Hospital and its staff did not follow the proper procedures.** That was the most substantial factor in our decision”.

“Various experts testified that the child should have been watched more carefully because he was **susceptible to hypoglycemia because of a condition his mother** had while pregnant. Instead, they testified the child received no nourishment during his first three days because he would not nurse. According to medical records, \_\_\_\_\_'s blood sugar level was zero when a test was finally taken three days after his birth. Shortly afterward, he suffered a seizure and was taken to \_\_\_\_\_ Hospital in \_\_\_\_\_”.

“\_\_\_\_\_ said she didn't think about filing a lawsuit until a few years after \_\_\_\_\_'s birth, **when doctors would not answer questions** she had regarding his brain damage”

(Source: <http://www.fansoffieger.com>; edited excerpt)

### Medico-Legal Considerations

- Know the risk factors for hypoglycemia
- Know the nursery's policies for screening and treatment
- Document presence of risk factors, diagnosis, treatment and response to treatment
- Communicate with nursery staff and parents

Fanaroff & Turbow *AAP Textbook of Pediatric Care*, 2008

### Summary and Conclusions

- Low plasma glucose is common after birth
- Hypoglycemia reflects inadequate metabolic adaptation during fasting
- Transient hyperinsulinism is the most common cause of persistent hypoglycemia beyond 12-24 hr

With new thinking, more is possible.



### Summary and Conclusions

- Hypoglycemia is a surrogate marker for low energy levels in the CNS
- Profound, prolonged and recurrent HG is associated with CNS injury
- Significance of brief HG without clinical signs is not clear
- Operational and therapeutic thresholds are likely unique to each neonate

With new thinking, more is possible.



### Summary and Conclusions

- Breastfeeding and frequent monitoring is sufficient for most full-term infants
- It is prudent to screen at-risk infants
- Long-term follow up is recommended for those needing intervention
- Documentation and communication are of paramount importance

With new thinking, more is possible.



### Acknowledgments

- Ivan Tkac
- Katie Czerniak
- Jonathan Gewirtz
- Phu Tran
- Pierre Gilles Henry
- Dinesh Deelchand
- Dustin Sperr
- Chris Traudt
- Michael Georgieff
- Kamil Ugurbil
- Betsy Seaquist
- NICHD
- Viking Children's Fund
- Minnesota Medical Foundation
- Graduate School

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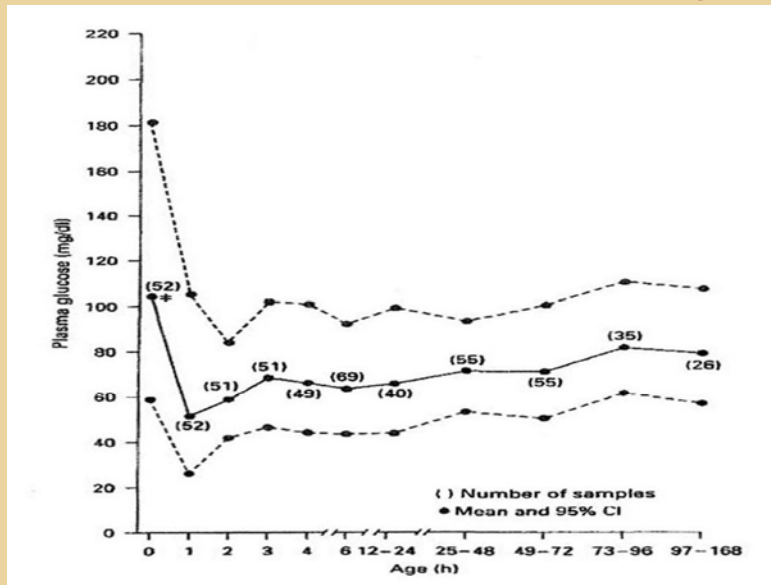
**TABLE 1 Most Prevalent Conditions Resulting in Malpractice Lawsuits (in Order of Frequency)**

| Condition                               | Average Indemnity (for All Claims), \$ |
|---|--|
| 1. Brain-damaged infant                 | 440 379                                |
| 2. Meningitis                           | 437 423                                |
| 3. Routine infant or child health check | 155 039                                |
| 4. Respiratory problems in newborns     | 270 607                                |
| 5. Appendicitis                         | 116 285                                |
| 6. Pneumonia                            | 239 531                                |
| 7. Specified nonteratogenic anomalies   | 186 708                                |
| 8. Premature birth                      | 250 031                                |
| 9. Birth                                | 286 407                                |
| 10. Asthma                              | 193 414                                |

McAbee et al., *Pediatr* 2008

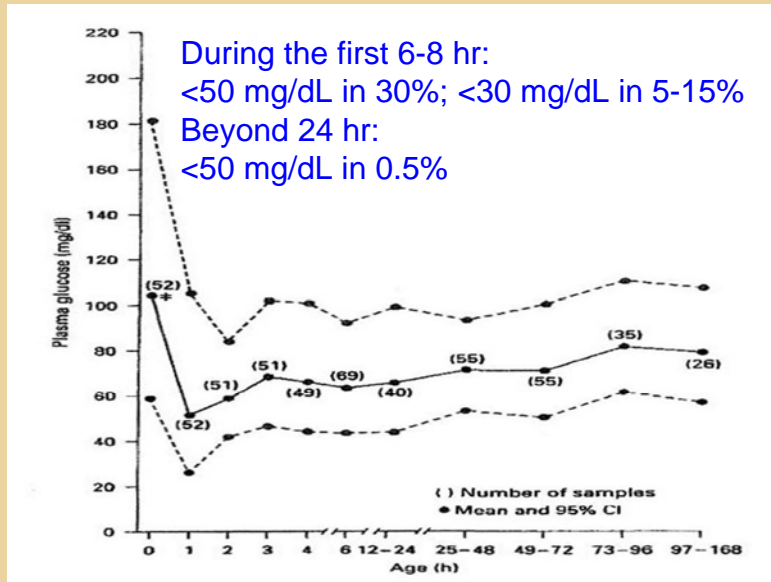


## Postnatal Blood Glc Changes



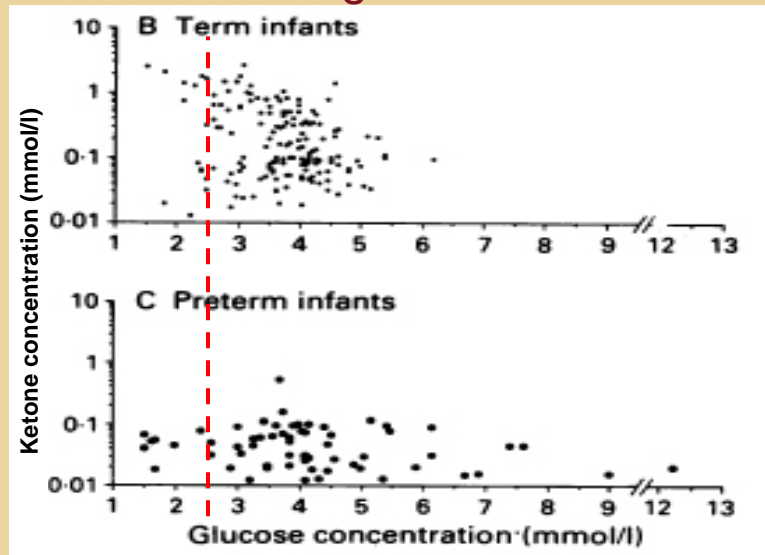
(Srinivasan et al., 1988)

## Postnatal Blood Glc Changes



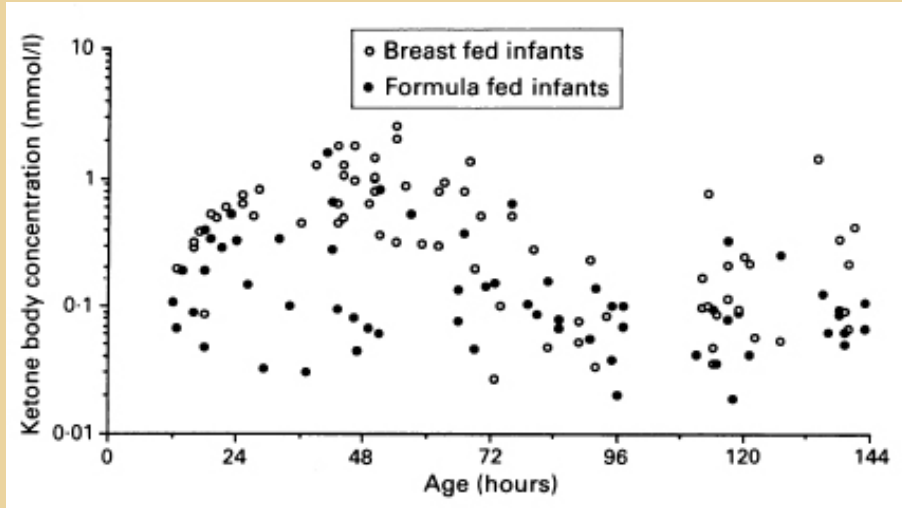
(Srinivasan et al., 1988; Lubchenco et al., 1971; Stanley et al., 1979)

## Gestational Age and Substrates



Hawdon et al., *Arch Dis Child* 1992

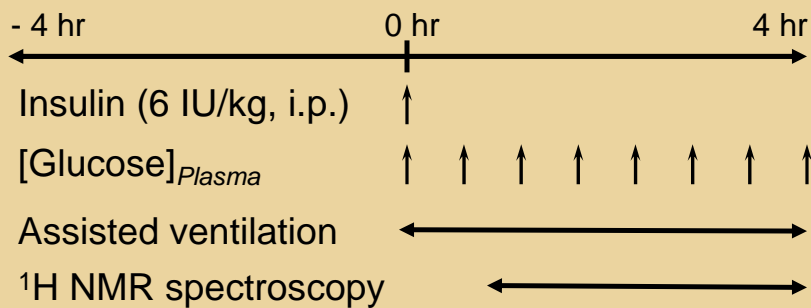
## Mode of Feeding and Energy Substrates

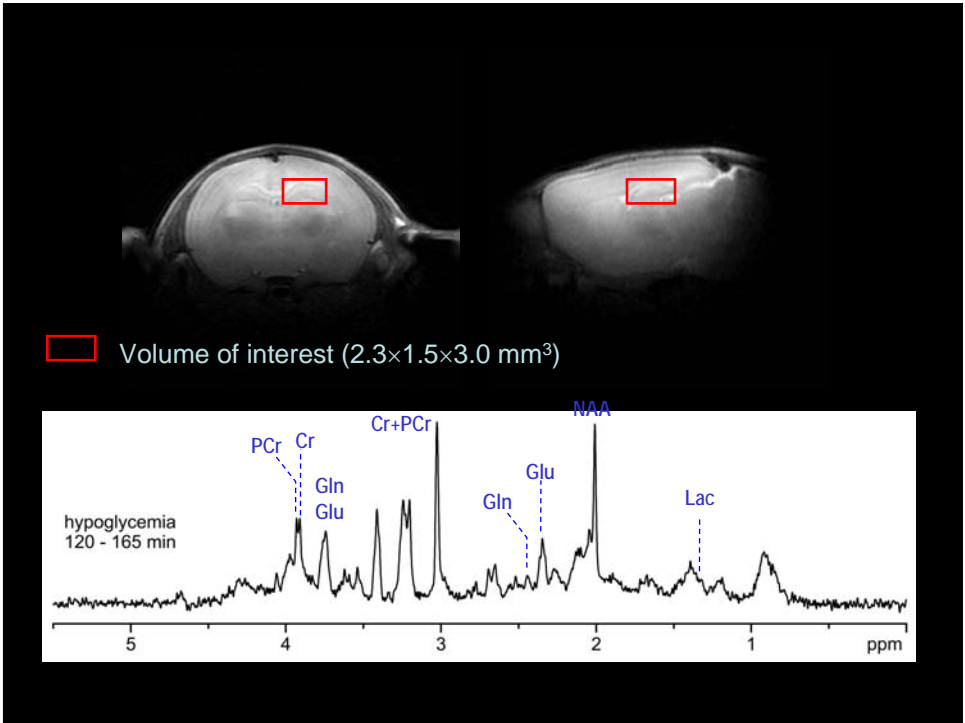
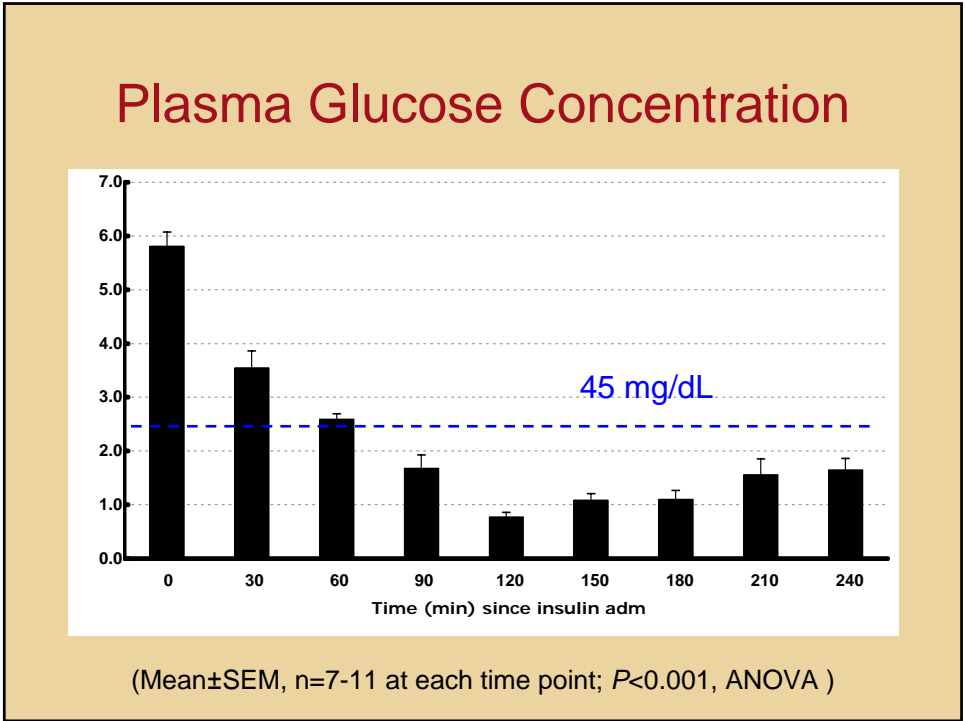


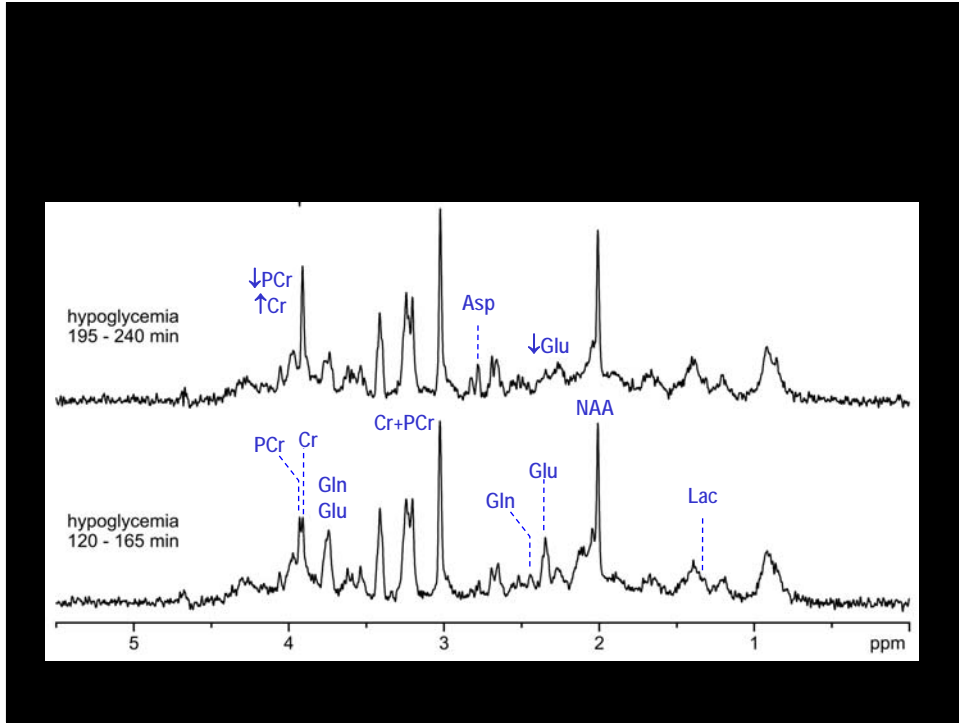
Hawdon et al., *Arch Dis Child* 1992

## Methods

14-day-old Sprague-Dawley rats (35 gm)







## Neurochemical Changes During HG

