Timely Identification of Neonatal Hypoglycemia

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Disclosures

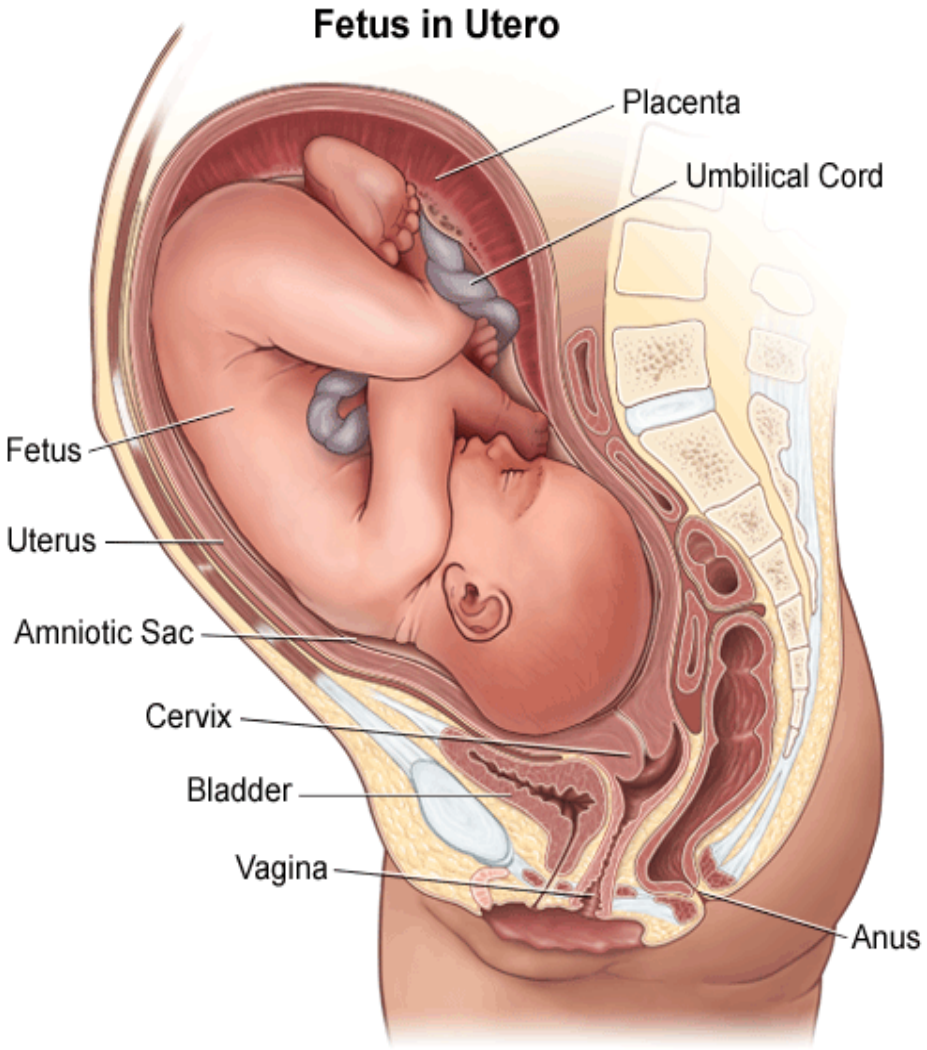
- Speaking Honoraria
  - Radiometer
  - Nova Biomedical
  - Draeger
  - Roche (Canada)
  - Alere (Canada)
- Research Support (Reagents, Instrumentation, Travel)
  - Nova Biomedical
  - Roche Diagnostics (Canada)
  - Radiometer
  - Instrumentation Laboratories (Canada)
- ALOL Biomedical Inc
  - Clinical Laboratory Consulting Business

Objectives

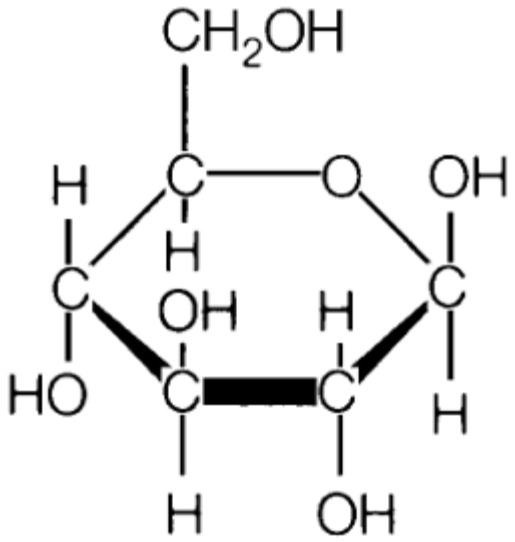
- Review the definition and incidence of neonatal hypoglycemia
- Describe why it is so important to identify neonatal hypoglycemia in a timely manner
- Discuss pre-analytical errors associated with the collection and handling of blood specimens that will affect the measurement of glucose

- Neonatal hypoglycemia was first described in 1929

- “Carbohydrate metabolism of premature infants” *Am J Dis Child* 1929:38;912-23



- The **fetus receives its entire supply of glucose** (70% of its energy needs) from the maternal circulation **via the placental transfer**

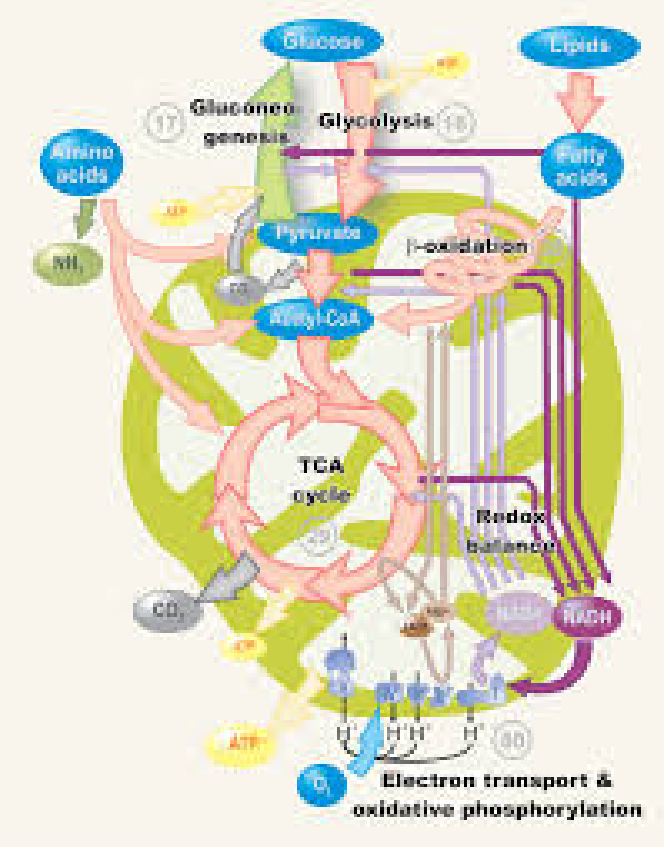


Glucose

- At **birth**, the **infant must supply its own glucose** needs

- **Hypoglycemia** in neonates, infants and children is essentially always a **problem** with **adapting to a “fasting” state**

- **Biochemical pathways** that **maintain "fuel"** during **fasting** are important to understand causes of hypoglycemia
  - Gluconeogenesis
  - Glycogenolysis
  - Ketogenesis



Neonatal Hypoglycemia

- ….”*is not a medical condition in itself but a feature of illness or* ***failure to adapt*** *from the fetal state of continuous transplacental glucose consumption to the extrauterine pattern of intermittent nutrient supply*”

Wight, 2006

Objective #1

- To review the definition and incidence of neonatal hypoglycemia

Objective #2

- To describe why it is so important to identify neonatal hypoglycemia in a timely manner

Objective #3

- To discuss pre-analytical errors associated with the collection and handling of blood specimens that will affect the measurement of glucose

Objective 1: Definition of Neonatal Hypoglycemia

1.6 mmol/L

(29 mg/dL)

2.6 mmol/L

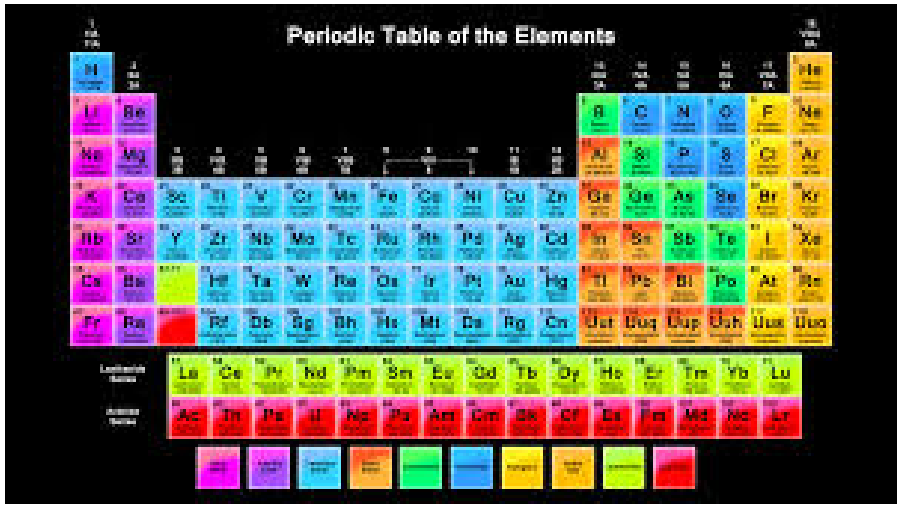
(47 mg/dL)

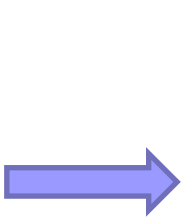
2.2 mmol/L
(40 mg/dL)

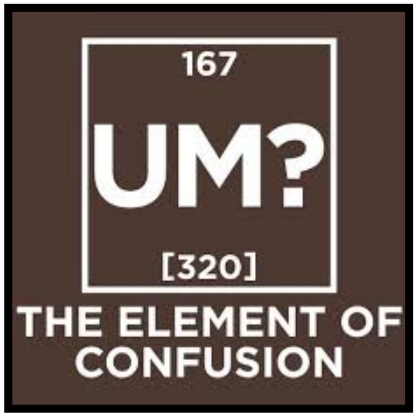
2.0 mmol/L
(36 mg/dL)

2.7 mmol/L
(49 mg/dL)

- **Definition of hypoglycemia** in the newborn is **controversial** because of a **lack of significant correlation** among **plasma glucose** concentration, **clinical symptoms** and long-term sequelae







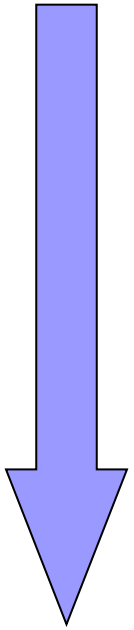
Neonatal Hypoglycemia

- No widely accepted definition
- Required blood [glucose] will be dependent upon:
    - Gestational age
    - Size
    - Energy requirements
    - Clinical Condition
- [glucose] where neurodevelopmental damage happens is variable (requires further investigation)

David Christiansen, Screening and Treatment of Neonatal Hypoglycemia, 2009. The Pas, Manitoba

Signs and Symptoms of Hypoglycemia

- Jitteriness
- Irritability
- Hypotonia
- Lethargy
- High-pitched cry
- Hypothermia
- Poor suck
- Tachypnea
- Cyanosis
- Apnea
- Seizures
- Cardiac arrest



[Glucose]

Verklan & Walden (2004) as cited by Amy Bloomquist Neonatal Hypoglycemia

What happens to glucose levels in healthy full term infants (breast fed) after birth?

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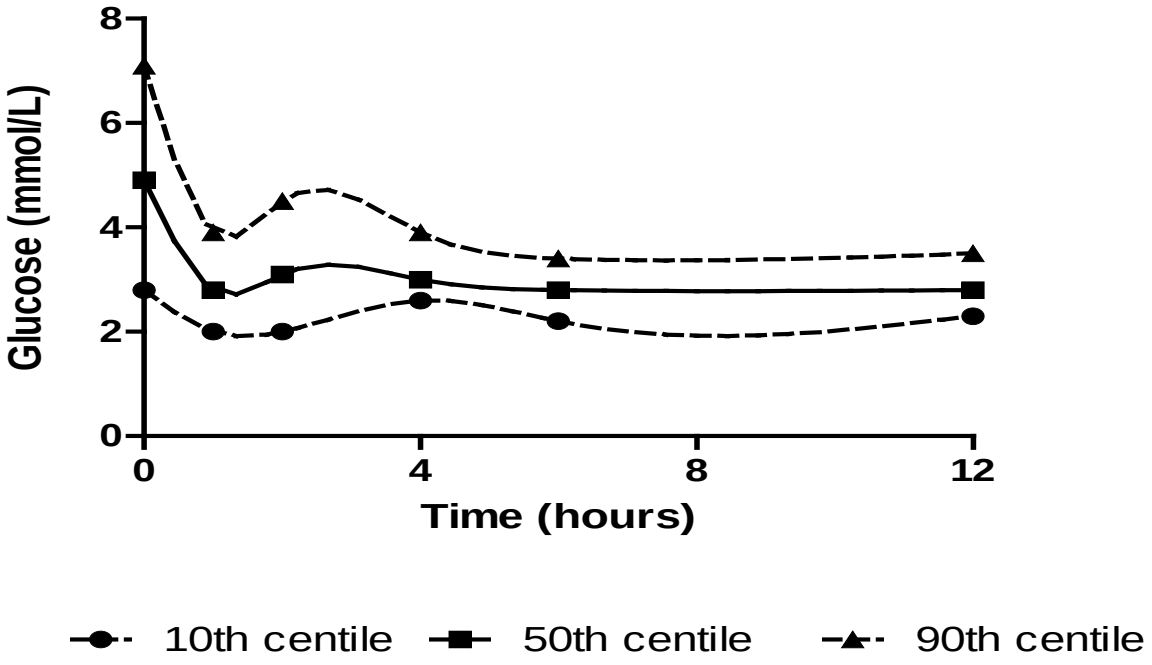
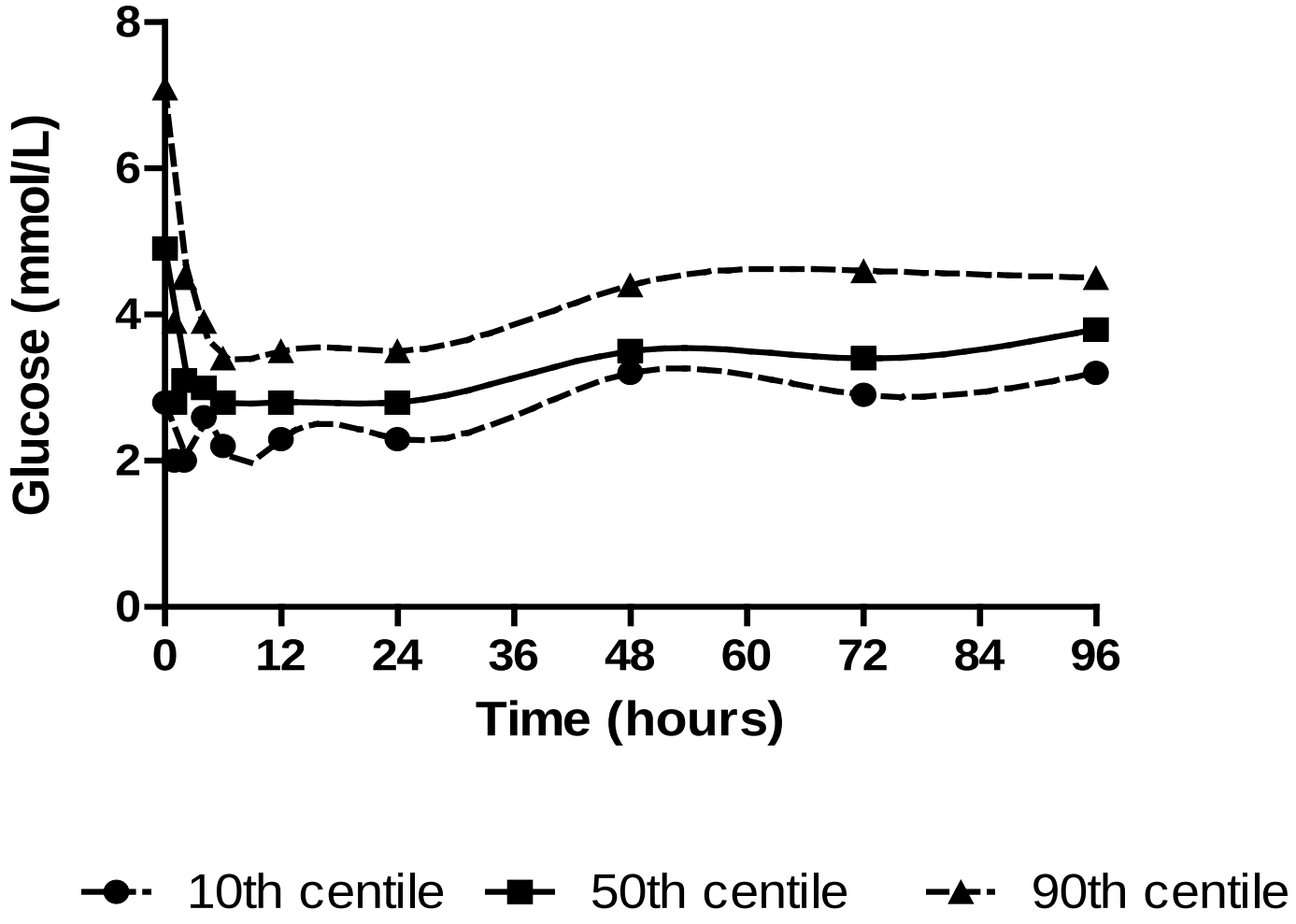


Hoseth, 2000


Glucose (mmol/L)
8
6
4
2
0
0
12
24
36
48
60
72
84
96
Time (hours)
10th centile
50th centile
90th centile

Neonatal Hypoglycemia

- Meta-analysis (term babies) Alkalay et al., Am J. Perinatology 2006: 23(2), 115-9
  - 5th percentile [glucose]
  - 1.6 mmol/L (29 mg/dL)(1-2 hr of life)
  - 2.2 mmol/L (40 mg/dL)(3-48 hr of life)
  - 2.7 mmol/L (49 mg/dL)(48-72 hr of life)

- World Health Organization

  Paediatric Child Health 2004: 9(10), 723-9 (Canadian Pediatrics Society Fetus and Newborn Committee)
  - < 2.6 mmol/L (47 mg/dL)
  - At- risk infants lead to short & long term neurological (imaging) changes

- "***Significant hypoglycemia*** *is not and* ***can never be defined as a single number*** *that can be* ***universally*** *to* ***every*** *individual* ***patient****. Rather, it is characterized by a value(s) that is unique to each individual and varies with both their state of physiologic maturity and influence of pathology*"

Cornblath et al., 2000

Operational Thresholds

- Represent “Action Values”
  - do not represent either normal or abnormal
  - prompt either further testing and/or treatment

- Operational threshold

Cornblath et al., Pediatrics 2000; 105(5), 1141-4

  - Always treat if <2.0 mmol/L (36 mg/dL);
  - desire [glucose] ≥ 2.6 mmol/L (46.8 mg/dL)

Incidence of Hypoglycemia

- Usually occurs in the first days of life
- Overall incidence = 1-5/1000 live births

Verklan & Walden (2004) as cited by Amy Bloomquist Neonatal Hypoglycemia

Incidence of neonatal hypoglycemia in babies identified as at risk

Harris DL, Weston PJ, Harding JE.
J. Pediatrics 2012; 161(5): 787-91

- Infants (n=514) (tertiary hospital)
  - ≥ 35 weeks gestation
  - Identified at risk of hypoglycemia
  - Blood [glucose] in the first 48 hrs of life

Incidence of neonatal hypoglycemia in babies identified as at risk

Harris DL, Weston PJ, Harding JE.
J. Pediatrics 2012; 161(5): 787-91

- 51% babies (260/514) became hypoglycemic (< 2.6 mmol/L; 46.8 mg/dL)
- 19% (97/514) had severe hypoglycemia (≤ 2.0 mmol/L; 36 mg/dL)
- 19% (98/514) had more than 1 episode
- 81% (315/390) of the hypoglycemic episodes occurred in the first 24 hours

Infants at Highest Risk for Hypoglycemia

- < 37 weeks gestation
- Infant of a diabetic mother
- Small for gestational age
- Large for gestational age
- Stressed/ill infants
- Exposure to certain medications
  - Treatment of preterm labor
  - Treatment of hypertension
  - Treatment of type 2 diabetes
  - Benxothiazide diuretics
  - Tricyclic antipressants in the 3rd trimester

Karlsen (2006) as cited by Amy Bloomquist Neonatal Hypoglycemia

At birth….

- “Fuel” requirements for the baby are achieved through a balance of
  - Exogenous sources (breast milk, formula)
  - Endogenous glucose production (glycogenolysis, gluconeogenesis)
  - Endogenous alternate fuels (ketones)

Objective 2

So ….why are we so concerned about glucose levels in the neonate?

“Cerebral glucose utilization accounts for 90% of the neonate’s glucose consumption”

Verklan & Walden (2004). Core Curriculum for Neonatal Intensive Care Nurses

“ *Compared with adults, infants have a higher brain to body weight ratio, resulting in higher glucose demand in relation to glucose production capacity*”

Objective 3

Pre-analytical errors associated with the collection and handling of blood specimens that will affect the measurement of glucose

Glucose meter:
2.9 mmol/L (52 mg/dL)

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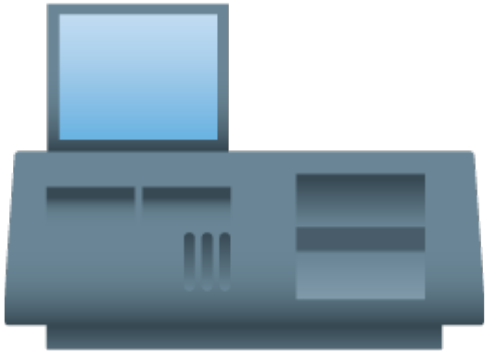
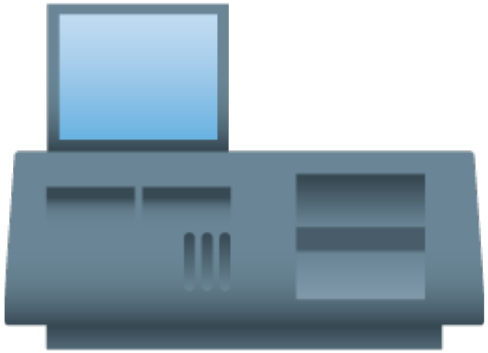
2.9 mmol/L (52 mg/dL)



Blood Gas Analyzer:
3.2 mmol/L (58 mg/dL)

Glucose meter:
2.9 mmol/L (52 mg/dL)



Blood Gas Analyzer:
3.2 mmol/L (58 mg/dL)

Clinical Lab (plasma hexokinase): 2.2 mmol/L (40 mg/dL)

Factors that can influence the measurement of glucose

- Type of blood tube (green top or grey top)
- Specimen temperature (to ice or not?)
- Time it takes from specimen collection to processing in the lab (ex vivo glycolysis)
- Capillary versus Venous specimens
- Interferences (Sugar Confusion)

Specimen Collection for Glucose Measurement

Heparin Tube

?

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Glycolytic Inhibitor Tube

Glucose Determinations in Plasma and Serum: Potential Error Related to Increased Hematocrit

Richard A. Sidebottom, Paul R. Williams, and Keith S. Kanarek

Clinical Chemistry 1982 vol 28 pp. 190-2

Table 2. Effect of Heparin, Fluoride, or No Anticoagulant on Glucose Values (mg/dL, mean ±SEM)

	Time after blood collection, hours				
	0	1	2	4	6
Infants					
Heparin	101 ± 2	90 ± 5	78 ± 6	63 ± 10	48 ± 7[a]
NaF	101 ± 2	93 ± 7	89 ± 6	88 ± 6	87 ± 6
Clotted serum	101 ± 2	[b]	90 ± 8	83 ± 7	80 ± 6
Adults					
Heparin	89 ± 4	83 ± 3	78 ± 3	67 ± 3[c]	57 ± 3[a]
NaF	89 ± 4	82 ± 3	80 ± 3	77 ± 3	75 ± 4
Clotted serum	89 ± 4	[b]	81 ± 3	73 ± 4	70 ± 4

[A] Decrement in glucose significantly greater in heparin-treated samples then in either NaF-treated or clotted samples, $p<0.05$. [b] Not measured. [C] Decrease in glucose significantly greater in the heparin-treated samples than in the NaF-treated samples, $p<0.05$

Rebuilt from original

To ice or not to ice the blood specimen?

Effect of Cooling the Blood Specimens

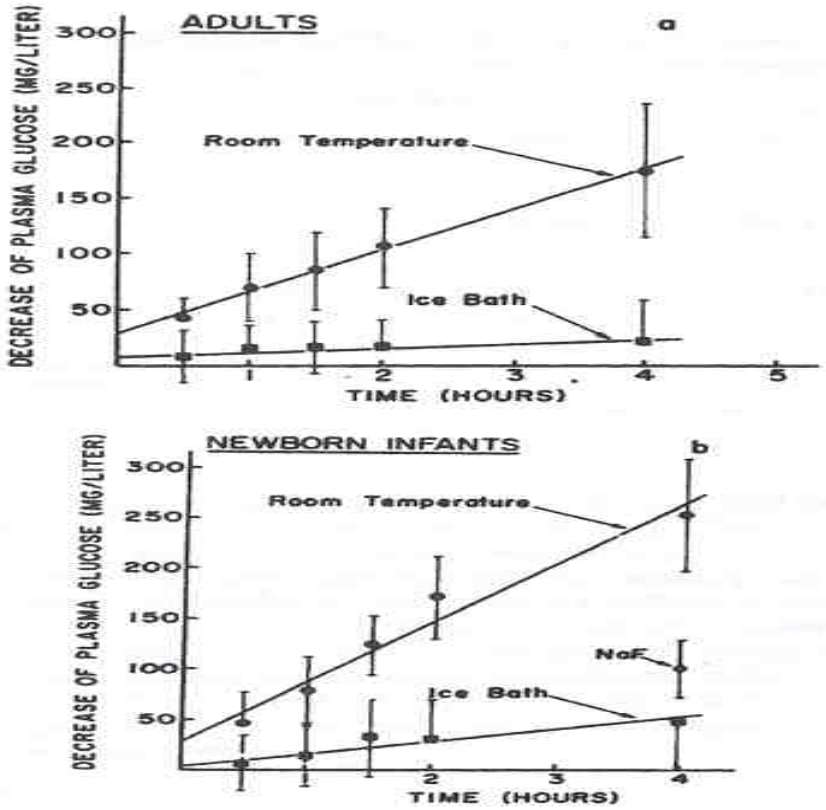


Fig. 1. Decrease in plasma glucose on storage of whole blood from (*a*) adults and (*b*) newborns

Bars are one standard deviation. Rates of decrease (slope, in mg/liter per hour) are: adults, room temperature, 36, ice, 3.9; newborns, room temperature, 60, ice, 11. In blood from newborn infants stored with NaF, the decrease at 4 h was intermediate between that of cooled blood and blood stored at room temperature without preservative

Effect of time between specimen collection and specimen processing

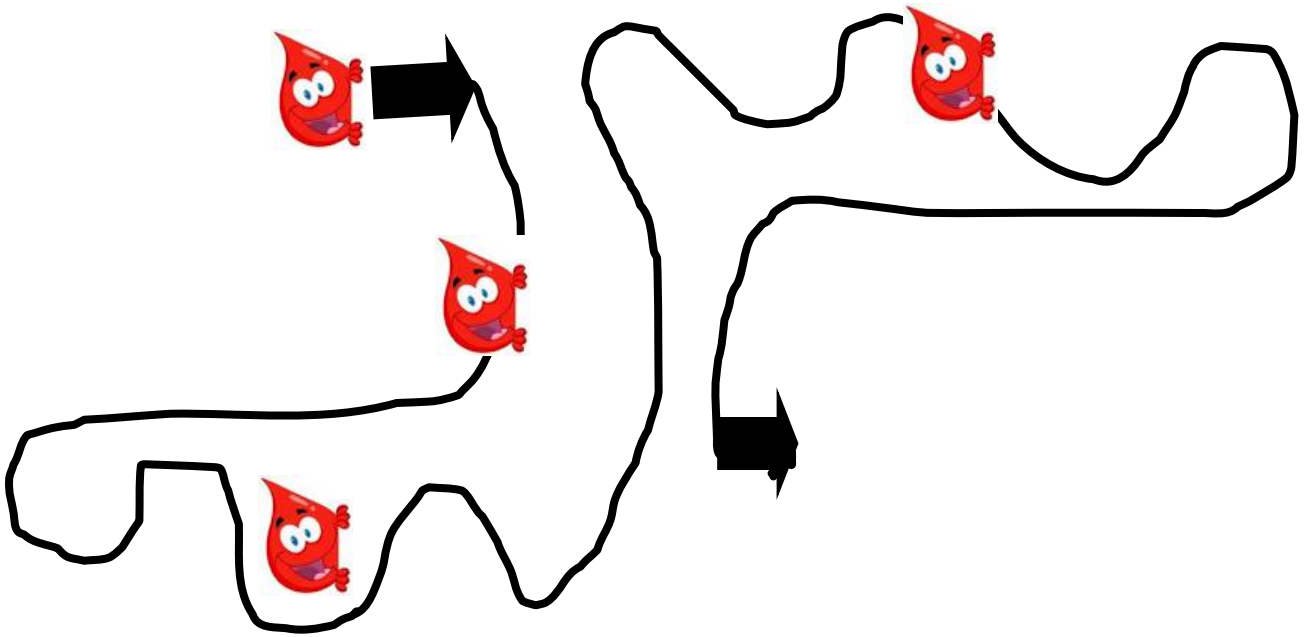


Table 1. Glucose changes with Increasing Hematocrit (Hct) and Time (hours)

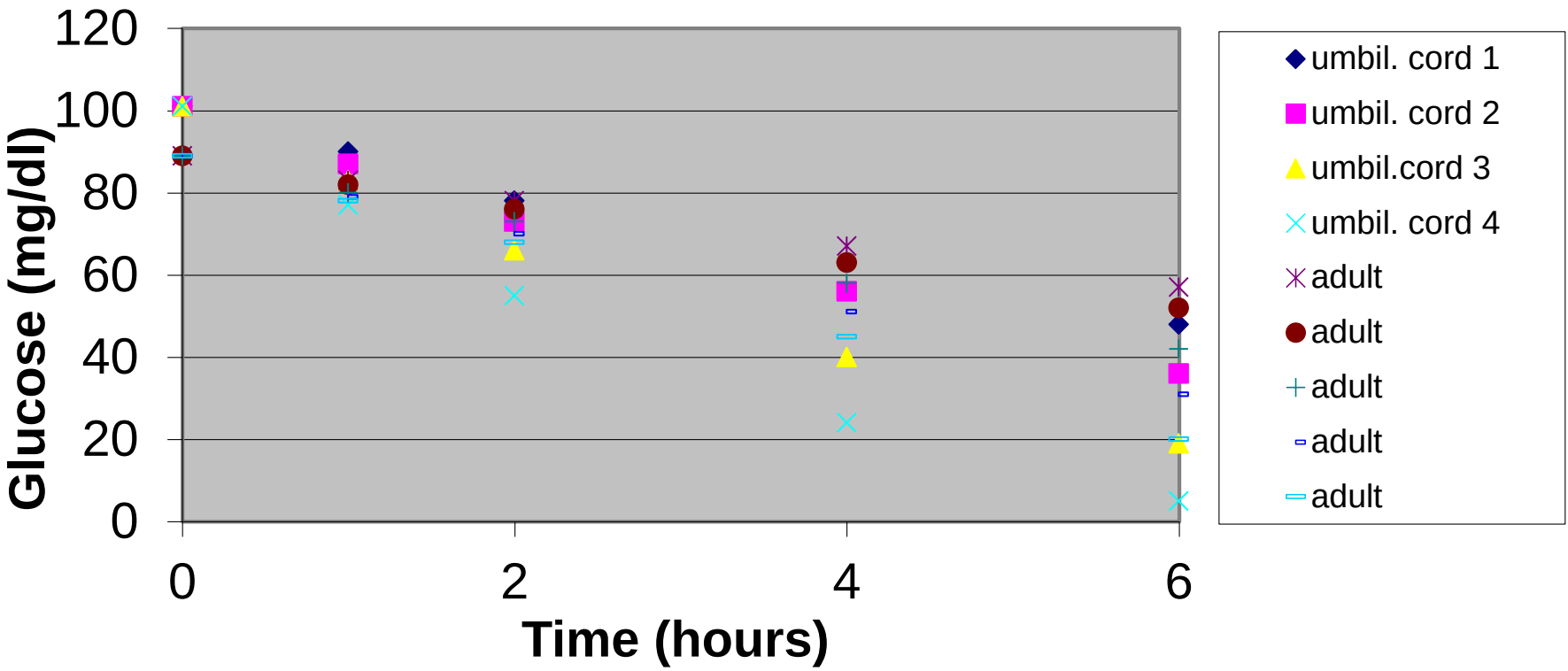
	Hct	0 hour	1 hour	2 hours	4 hours	6 hours
Adult group 1	0.43	89 ± 4[a]	83 ± 3	78 ± 3	67 ± 3	57 ± 3
Adult group 2	0.51	89 ± 4	82 ± 3	76 ± 3	63 ± 2	52 ± 2
Infant group 1	0.51	101 ± 2	90 ± 5	78 ± 6	63 ± 10	48 ± 7
Adult group 3	0.60	89 ± 4	80 ± 3	73 ± 3	58 ± 3	42 ± 3
Infant group 2	0.60	101 ± 2	87 ± 4	73 ± 5[b]	58 ± 5[b]	36 ± 6[b]
Adult group 4	0.68	89 ± 4	79 ± 3	70 ± 2	51 ± 2	31 ± 3
Infant group 3	0.71	101 ± 2	83 ± 5	66 ± 5[b]	40 ± 6[b]	19 ± 5[b]
Adult group 5	0.75	89 ± 4	78 ± 3	68 ± 2	45 ± 2	20 ± 3
Infant group 4	0.81	101 ± 2	77 ± 5[b]	55 ± 5[b]	24 ± 5[b]	5 ± 3[b]

[a]All glucose values expressed in mg/dL (mean± SEM), [b]Difference between the adult group and infant group at comparable time and hematocrit is significant p,0.05 or less

Please note: Specimens were collected into sodium heparin

Rebuilt from original

Glucose Changes Over Time

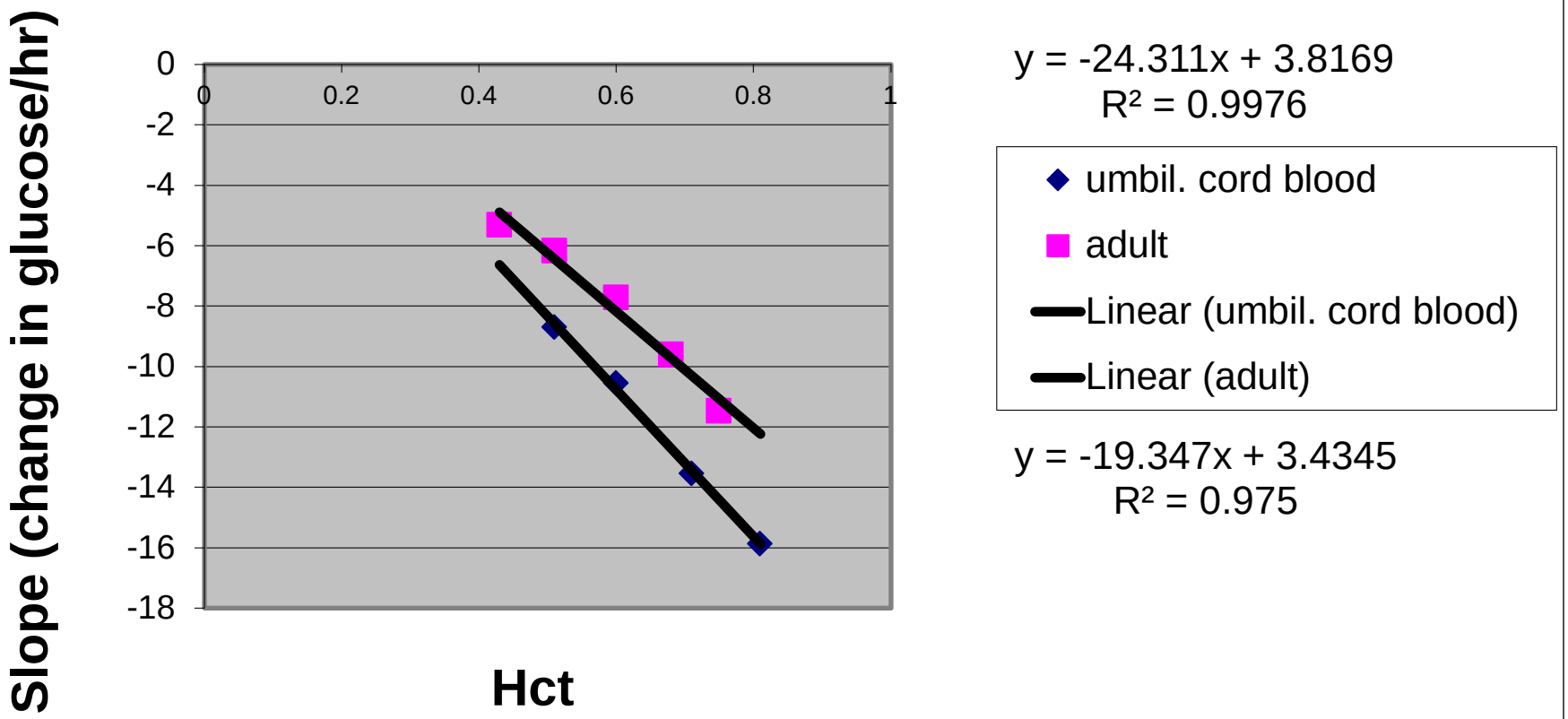


Regression Lines

Umbilical Cord 1	y =-8.7069x + 98.638	R^2 = 0.9892	Hct = 0.51
Umbilical Cord 1	y =-10.552x + 98.034	R^2 = 0.99	Hct = 0.60
Umbilical Cord 1	y =-13.552x + 97.034	R^2 = 0.9884	Hct = 0.71
Umbilical Cord 1	y =-15.87x + 93.664	R^2 = 0.9695	Hct = 0.81
Adult 1	y =-5.319x+ 88.629	R^2 = 0.9993	Hct = 0.43
Adult 2	y =-6.172x + 88.48	R^2 = 0.9985	Hct = 0.51
Adult 3	y =-7.724x + 88.483	R^2 = 0.9993	Hct = 0.60
Adult 4	y =-9.612x + 88.991	R^2 = 0.9998	Hct = 0.68
Adult 5	y =-11.466x + 89.81	R^2 = 0.9986	Hct = 0.75

Rebuilt from original

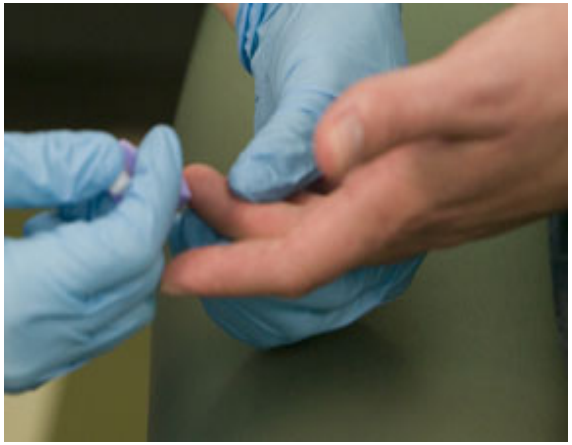
Slope versus Hct



Infant cord blood 1.35 mmol/L/hr

Adult blood 1.07 mmol/L/hr

Capillary versus Venous Specimen



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Capillary versus Venous Specimen

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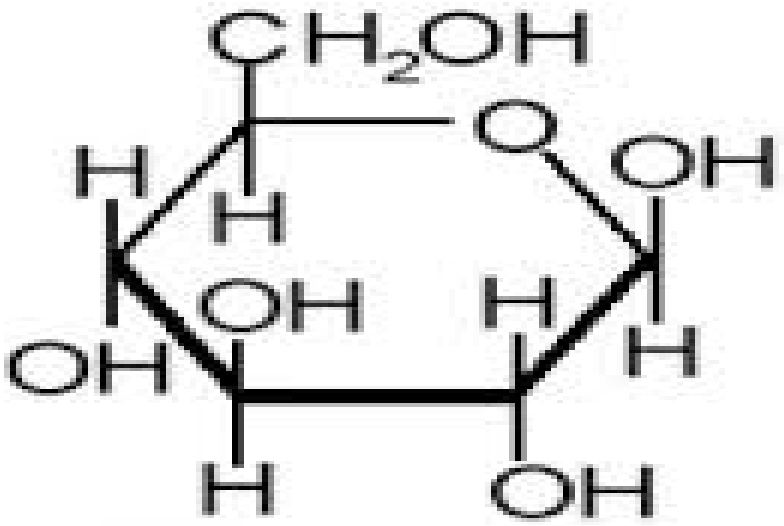
Capillary glucose can be up to 20-25% higher than venous glucose

Capillary versus Venous Specimen

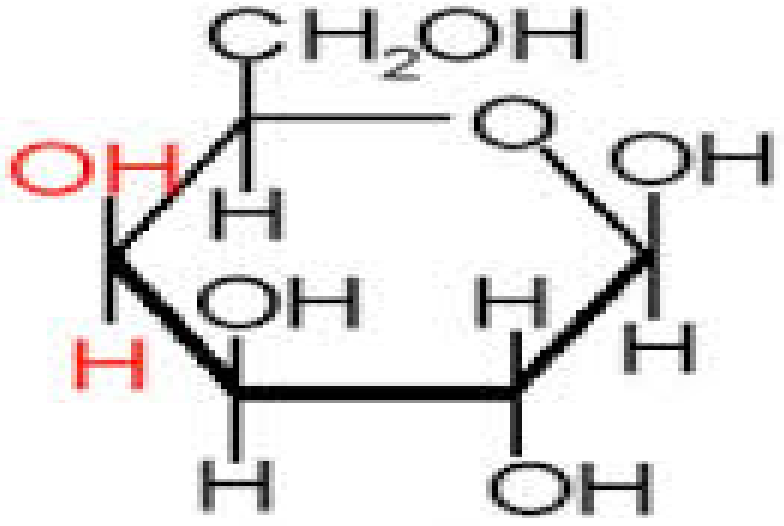
=

ONLY FOR A FASTING SPECIMEN !!

Sugar Confusion

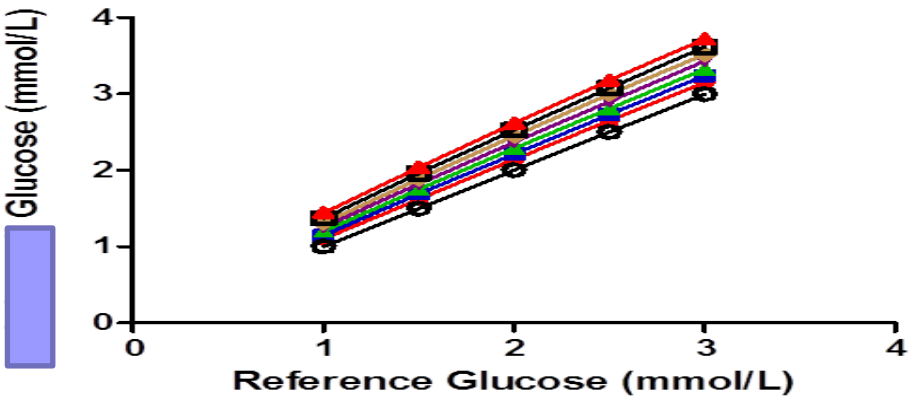


Glucose



Galactose

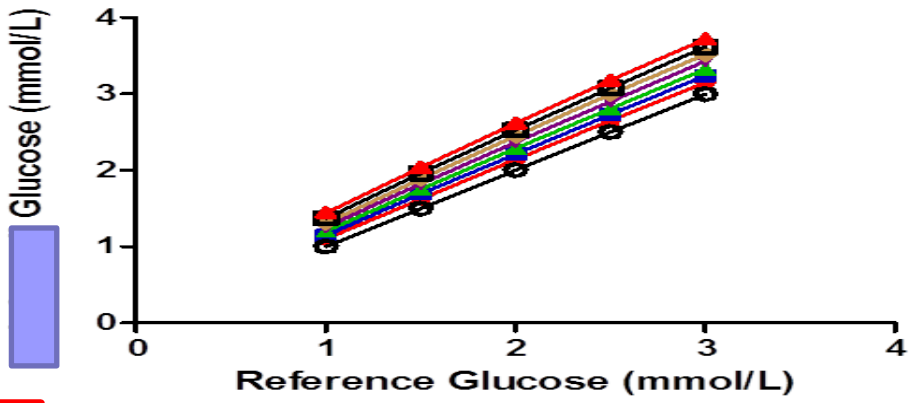
Effect of Low Galactose Concentrations on the Performance of the [redacted] Glucose meter



Galactose Concentration (mmol/L)

Reference Glucose (mmol/L)	0	0.2	0.4	0.6	0.8	1.0	1.2	1.4
1.0	1.0	1.10	1.15	1.20	1.26	1.31	1.37	1.44
1.5	1.5	1.62	1.69	1.75	1.82	1.89	1.96	2.04
2.0	2.0	2.14	2.21	2.29	2.37	2.45	2.53	2.62
2.5	2.5	2.65	2.73	2.81	2.90	3.00	3.08	3.18
3.0	3.0	3.15	3.24	3.33	3.43	3.52	3.62	3.72

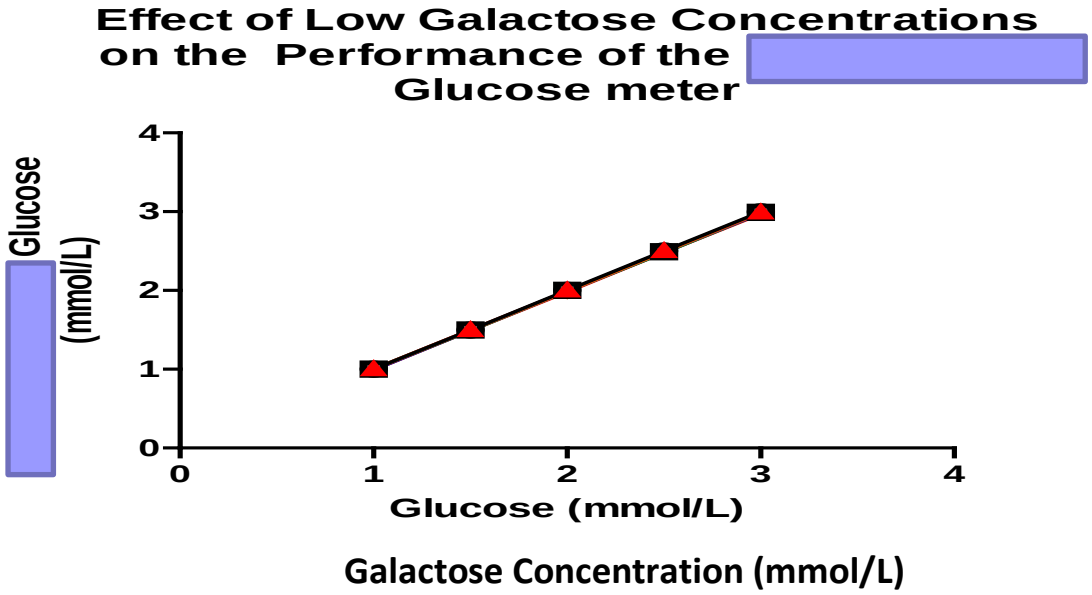
Effect of Low Galactose Concentrations on the Performance of the Glucose meter



mg/dL

Galactose Concentration (mmol/L)

Reference Glucose (mmol/L)	0	3.6	7.2	10.8	14.4	18.0	21.6	25.2
18	18	19.8	20.7	21.6	22.7	23.6	24.7	25.9
27	27	29.2	30.4	31.5	32.8	34.0	35.3	36.7
36	36	38.5	39.8	41.2	42.7	44.1	45.5	47.2
45	45	47.7	49.1	50.6	52.2	54.0	55.4	57.2
54	54	56.7	58.3	59.9	61.7	63.4	65.2	67.0



Reference Glucose (mmol/L)	0	0.2	0.4	0.6	0.8	1.0	1.2	1.4
1.0	1.0	0.99	0.99	1.00	1.00	1.00	1.00	1.00
1.5	1.5	1.49	1.49	1.49	1.50	1.50	1.50	1.50
2.0	2.0	1.98	1.99	1.99	1.99	1.99	2.00	2.00
2.5	2.5	2.48	2.48	2.48	2.49	2.49	2.49	2.50
3.0	3.0	2.97	2.98	2.98	2.98	2.99	2.99	2.99

Effect of Low Galactose Concentrations on the Performance of the Glucose meter

mg/dL

Galactose Concentration (mmol/L)

Reference Glucose (mmol/L)	0	3.6	7.2	10.8	14.4	18.0	21.6	25.2
18	18	17.8	17.8	18	18	18	18	18
27	27	26.8	26.8	26.8	27	27	27	27
36	36	35.6	35.8	35.8	35.8	35.8	36	36
45	45	44.6	44.6	44.6	44.8	44.8	44.8	45
54	54	53.5	53.6	53.6	53.6	53.8	53.8	53.8

Legal Consequences of Missing a Neonatal Hypoglycemia

TOLL-FREE 888.330.8312

SAN FRANCISCO 415.992.3744

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Failure to Recognize Neonatal Hypoglycemia - $2,250,000 Settlement

Our attorneys obtained a mediated settlement of $2,250,000 on behalf of a male infant who now suffers from blindness, developmental delay and cognitive deficits, and who also had his pancreas removed, after nursing staff failed to follow proper protocols when the infant showed signs of hypoglycemia. The infant was born weighing 10 pounds, 7-1/2 ounces, which should have triggered blood screening tests at one, two, four, six and eight hours of age. Any tests revealing low blood sugar levels required that a blood sample be drawn and sent for analysis. In this case, the infant's six-hour test was conducted at seven hours of age, and came back showing low blood sugar. However, the protocol requiring that blood be drawn and sent to the lab was not followed. The infant's parents were never told of the abnormal result or warned to look for signs of hypoglycemia. At 24 hours of age, the infant and his parents were discharged. On the second morning at home, his mother had a hard time rousing him, and he presented at Urgent Care lethargic, not nursing, and with purple feet. He then suffered several seizures and was admitted to the hospital. Tests revealed

Settlement for Newborn's Brain Damage Is $4 Million in Rhode Island

2010 Medical Malpractice Trial Report

Medical Malpractice Lawsuit Contends Baby's Brain Damage Due to Negligency in Newborn Nursery

The minor plaintiff was born on 9/8/05 in a Rhode Island hospital. He was a healthy, normal baby. He had some difficulty latching on for breast feeding, so a hospital pediatrician ordered that his breastfeeding attempts be supplemented with formula. That order was not followed by the nurses, and the baby became hypoglycemic with a critically low glucose level of 5. Head studies showed brain damage due to hypoglycemia. Today, the boy is 5 years old and suffers from vision problems, a tactile sensory disorder, and developmental delays.

The plaintiff contended that the maternity nurses caring for the baby breached the standard of care when they failed to appreciate the baby's increased risk for hypoglycemia despite his marginally low birth weight as well as an episode of "jittery" behavior, his difficulty maintaining his body temperature after birth, his difficulty in latching on for breastfeeding, and his poor oral intake; when they failed to obtain frequent blood glucose levels on the baby; and when they failed to supplement feedings for the baby. The plaintiff claimed these violations of the standard of care resulted in hypoglycemia which has caused permanent neurological injuries and impairments.

The defendants contended that the boy's injuries are limited and that he

NHS failings that left babies with brain damage set to cost £235m

NHS Litigation Authority sets aside £235.4m to settle 60 cases in which hospital staff failed to spot hypoglycaemia in newborns

Denis Campbell, health correspondent
The Guardian, Monday 9 April 2012 20.59 BST

Newborn babies at risk of hypoglycaemia should be monitored using a heel prick blood test every few hours, according to Department of Health advice. Photograph:

Society
NHS · Health · Midwifery
UK news
More news

More on this story
NHS chief to investigate overnight discharges

Queen asked to intervene in NHS diamond jubilee pay

Conclusions

- No widely accepted definition of neonatal hypoglycemia currently exists
- Incidence of hypoglycemia for “at risk” infants is profound
- Measurement of glucose level is complicated
  - Numerous factors can influence the measurement (tubes, temperature, length of time before specimen processing, interfering substances)