HYPOGLYCEMIA IN INFANTS AND CHILDREN

A PRACTICAL APPROACH

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This morning what I’d like to do is try to have you understand that glucose homeostasis is a very dynamic process, and that there are factors that affect glucose concentrations that really affect its rate of appearance and its rate of disappearance into the plasma space. And have you understand that there are some unique aspects of glucose homeostasis in the pediatric population. And briefly relate this rate of appearance and disappearance to some pathophysiologic problems that we face in clinical practice. And then focus on hypoglycemic awareness in the diabetic patients, which is probably the population that we see most hypoglycemia in. And finally to reemphasize to you again and again and again the importance of obtaining the critical value at the time the child presents with hypoglycemia, which will lead us in the diagnostic pursuit of an etiology, and hopefully avoid recurrence and preserve neurologic function for that child.
Glucose exists in a pool in the extracellular space. And it enters into the pool through several pathways, from diet, through hepatic and kidney sources, and it’s used by peripheral tissues. One can get hyperglycemic by either decreasing the rate of flow out of the system, or increasing the rate of flow into the system. Conversely, if one looks at hypoglycemia, by increasing the rate of disappearance of glucose from the plasma space, you will have a fall in the blood glucose concentration, or if the rate of appearance or the rate of production of glucose in the body decreases, once again you have a situation in which the rate of appearance is less than the rate of disappearance, and what happens is, the concentration falls.
Now there are some differences in the pediatric, adolescent, and adult individual with regards to plasma pool sizes and kinetics of glucose. If you take an individual who has a blood sugar of about 90 mg/dl, or 5 mmol, the glucose is distributed in about 25% of the body weight, which gives you a total pool of glucoses of about 100 mmol. If you take an early adolescent young individual with the same concentration, they have the same distribution, just on the basis of weight difference their pool size is much smaller. If you take a young child of about 15 kilograms, it’s even smaller. Again, the pool sizes are the same. But when you look at an infant, the pool size is, in fact, a little bit larger because the distribution of the glucose is higher in the newborn infant, even at the same glucose concentration. But because the weight is smaller, the amount of glucose is significantly smaller. If you translate that into some common measures, we’re talking about an adult – those here in the audience who are not diabetic have about four teaspoons of sugar circulating, or about 20 grams, whereas the newborn has about 1 gram of glucose circulating. And so the amount of glucose that’s available under certain circumstances is dramatically different.
There are also some differences in the kinetics in these same individuals. Adults have a glucose turnover rate of about 10 micromoles per kilo per minute, or about 2 mg/kg/min. Children from infancy up through about the age of eight or nine have a glucose turnover rate of about 6 mg/kg/min. This is an important number to remember when you’re dealing with IV glucose fluid administration rates. If one was to suddenly discontinue the rate of entry of the glucose by some artificial means, we can look at what the half-life would be in terms of glucose. In the adults it gives you about a half-life for the glucose to fall from 90 to 45 of about 80 to 90 minutes. Whereas in the child it’s more like 30 minutes, even when one considers the differences in body size, because of this higher turnover rate. So the child, and the infant particularly, are much more prone to hypoglycemia just on the basis of the kinetic nature and the pool sizes that are available.
Now we can partition, knowing how much glucose is generally used by the brain, we can partition the amount of glucose that’s used by the brain at any particular age or size. And in the newborn the vast majority of the glucose is used by the brain because the brain is so much larger than the rest of the body. And what isn’t used by the brain then must be used by some other body tissue, and as you can see, a very small amount in the newborn is used by the peripheral tissues. As the child grows in size, the brain to body weight ratio changes, and the amount of glucose used by non-brain tissue increases. But nonetheless, even out in adult populations, 40% or so of glucose turnover is used exclusively by brain. So it becomes a major organ of utilization, and when it becomes limiting to brain availability, we get symptoms. And as Dr. Fishman just talked about, seizure disorders can occur.
Now after an overnight fast, we used to think that the vast majority of the glucose that was being delivered into the systemic circulation was coming from hepatic glycogen. Well, in fact, that’s not true. We now have techniques to be able to measure that. And we know that the vast majority of glucose being produced after an overnight fast is coming by way of the process of gluconeogenesis and a smaller proportion is coming from glycogenolysis. Now at the time of a meal, glucose enters into the systemic circulation and raises the glucose concentration, which then increases the arterial glucose exposure to the beta cell, which increases insulin secretion, and insulin then has some very dramatic effects on our little pool model here. The first thing it does is, it shuts off hepatic glucose production. So it decreases the rate of entry of glucose into the pool. It also restores the glycogen pools that have been depleted after an overnight fast. Then it increases glucose utilization by muscle and by fat and increases the rate of disappearance, returning the blood glucose concentration back towards normal. So this dynamic event occurs every single minute that we are awake without thinking one iota about what’s happening. It’s only when the system gets broken do we have problems in managing patients.
Now in the fed state – this is a schematic representation of glycogen in the Embden-Meyerhof pathway or gluconeogenic pathway – when one consumes glucose, glucose enters predominantly into this pathway and is forced into glycogen and then down the pathway for oxidation and for fat formation. However, the vast majority of glucose escapes the liver on ingestion and ends up in the peripheral circulation. And when that happens, there’s increased insulin, there’s a decrease in suppression of fatty acids, and fatty acid oxidation at the level of the liver and the formation of ketone bodies is in fact the energy source that drives gluconeogenesis. So in doing this we decrease the drive for gluconeogenesis by reducing the fatty acid availability. With increased amounts of insulin then, we have increased transport of glucose. We have less fatty acids available. In the overnight fast, most of muscle uses fatty acids, and so we switch that to glucose metabolism, and with less ketone bodies then, exclusively the brain uses glucose. And this is an important issue we’ll get to in a second, the utilization by the brain of ketone bodies.
Now if one was to take a group of individuals and fast them, we find that their responses are different, depending on whether they’re adults or children and whether they’re men or women. You fast men out for a period of about four days, you find their blood sugar concentrations fall. They don’t become hypoglycemic. Women become a little less hyperglycemic than do men, they are a little more hypoglycemic. And if you fast children, they keep up for about the first 14 to 18 hours of fasting, and then they plummet down to a blood glucose concentration of about 52 here at 30 hours.
If we look at the hormonal responses in terms of insulin, following the supper meal, insulins are stimulated. They fall. And as one has a relationship between hyperglycemia and insulin concentrations, the men have the higher concentrations, have higher insulins than do women, and the children have lower. If we look at glucagon, which is a primary counter regulatory hormone to insulin action, it’s increased after a meal because of an artifact. But after a period of fasting, you see the glucagon concentrations go up. That drives hepatic glucose production and the release of glucose from glycogen and stimulates gluconeogenesis. An important physiologic role that is paralyzed in the patient with type I diabetes.
Now as the glucose falls, fatty acids are mobilized from our fat stores. One of the things that we as adults like to do when we want to lose some weight. But if you are fasting, the fatty acids go up. They are burned by the liver. And one gets the development of ketonemia. And if one looks, children become as ketotic as women – after 30 hours of fasting – as women do after probably two to three days of fasting. And men never become as ketotic as children after a short period of fasting. So, ketone body availability is extraordinarily important because the brain has the capacity to use ketone bodies to supplant some of the glucose utilization by brain. And therefore a ketotic individual, even if they have low blood glucose, probably has more substrate available than one who is not ketotic at the same blood sugar level.
Now fatty acids play a key role in our sink model here, from the standpoint that in fasting, all of the substrate is coming out of the liver. Some is coming from the kidney. And as one fasts, there are increased fatty acids. The increased fatty acids drive the process of gluconeogenesis, and they create ketone bodies, and the fatty acids themselves are used by muscle, and the ketone bodies can be used by brain. In doing that, one reduces the amount of glucose that is necessary for both of these tissues under these circumstances. So one spares glucose under these circumstances by burning fatty acid. So the fact that one gets ketotic is in fact an advantage in terms of glucose homeostasis.
Now setting aside the child, the infant, and the adult, the newborn is in a particularly vulnerable position. And that is, that the newborn in utero, up until the time of delivery, has absolutely no glucose produced by the liver or by the kidney endogenously. All of the glucose is derived by transplacental transport. And what happens is, when we very kindly clamp the cord, we then stop the glucose infusion into the infant; and in fact what happens is that the glucose concentration falls. And only after a short period of time does glucose production begin. And the infant is born with the highest glycogen concentrations they will ever have. That’s a term infant. So they have very high glycogen content that is available to be mobilized in the first hours of life. Now that’s not true for a premature infant because the accumulation of glycogen stores occurs over the last four to five weeks of gestation. As the glucose production rate increases, the glucose concentration rises again. But it isn’t really until the child begins to take in adequate calories, and particularly carbohydrate intake, that one is able to return the glucose up to a normal concentration. And that usually occurs after three to four days of life. So how does this translate if one looks at it?
These are not year 2000 data; these are data from 1953. They are just as pertinent today as they were then. There is a difference between whole blood and plasma glucose concentrations. At delivery the glucose concentration is very close to that of the maternal plasma glucose at the time. Because there’s no hepatic production, the glucose concentration falls. As hepatic production turns on, it flattens this fall. But it really isn’t until day two of three that the glucose concentration gets up into an 80 to 90 mg/dl range. So the newborn infant is particularly vulnerable because they do not have a previous history of hepatic glucose production that they can fall back on, as you and I have after an overnight fast.
What is Hypoglycemia

- Depends!!!
  - 1 hr post prandial?
  - 84 hr fasting?
- Usually defined in the Post-absorptive State
  - < 40 mg/ dl (2.2 mM) Plasma
  - < 35 mg/ dl (1.9 mM) Whole Blood
- If electively fasting a child
  - < 50 mg /dl (2.8 mM) observed very closely
  - < 40 mg/ dl (2.2 mM) draw diagnostic blood
    (± Tolerance test)

So what is hypoglycemia? We’ve been debating this ever since somebody measured blood sugar. Is it an hour after you eat a meal, or is it after you’ve fasted for 84 hours? Well, so you need to be careful about how you define this. We generally define it in the postabsorptive state after an overnight fast, and it’s a blood sugar of less than 40 mg/dl, or 2.2 mmol, or 35 mg/dl of whole blood, 1.9 mmol. But if you are electively fasting a child to see if they are hypoglycemic, I really get very nervous at about a blood sugar of 50 and watch very closely at the bedside until we get that magic number of 40, and then I stop the fast or carry out the tolerance test if that’s what been planned for the child’s evaluation.
These are the signs of hypoglycemia in the newborn. They’re all familiar to you, I know. And you also know how specific they are. They are specific for hypoglycemia, sepsis, cardiovascular disease, neurologic disease, and hypocalcemia. That is, we have a high index of suspicion for these kinds of problems when you see these kinds of symptoms. And oftentimes it’s either the mother or the nurse that will alert the house officer or the physician that there’s a problem, which should trigger a response of, “Let’s get some things evaluated.”

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<th>Signs of Hypoglycemia Newborn Infant</th>
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<tr>
<td>• Jitteriness (Tremor)</td>
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<td>• Pallor</td>
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<td>• Cyanosis</td>
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<td>• Too quiet</td>
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<td>• Grey appearance</td>
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<tr>
<td>• Poor suck</td>
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<tr>
<td>• Hypothermia</td>
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<td>• “acting funny”</td>
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<th>Non-Specific Response with a wide differential diagnosis</th>
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<tr>
<td>• Hypoglycemia</td>
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<tr>
<td>• Sepsis</td>
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<tr>
<td>• Cardiovascular Disease</td>
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<tr>
<td>• Neurological Disorders</td>
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<tr>
<td>• Hypocalcemia</td>
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Now here’s a compendium of transient causes of hypoglycemia in the newborn, and I’m not really going to spend any time on it. The ones you will see clinically are the SGA infant, which from physical exam you should be aware of, and even from ultrasonography you should be aware of. The infant of the diabetic mother we still see, but as the control of the gestational diabetic or the type I diabetic mother has improved, the risks for hypoglycemia in the infant have decreased. These others are ones that hopefully we don’t see at all anymore, or only rarely. Because the mechanisms are not intact, or as not solidly intact, in the newborn, if one discontinues a high rate of glucose infusion in the infant, it’s no different than if you clamped the cord. There’s a rapid fall in glucose and you have decreased ability to counter-regulate, and you will see hypoglycemia. And these other issues are also ones that one needs to be aware of in dealing with newborn infants.
**Symptoms and Signs of Hypoglycemia in the Older Child or Adult**

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<th>NEUROGENIC (autonomic)</th>
<th>NEUROGLYCOPENIC</th>
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<td><strong>Cholinergic</strong></td>
<td>Warm</td>
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<tr>
<td>Sweaty</td>
<td>Weak</td>
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<tr>
<td>Hungry</td>
<td>Difficulty Thinking / Confuse</td>
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<tr>
<td>Tingling</td>
<td>Tired / Drowsy</td>
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<tr>
<td><strong>Adrenergic</strong></td>
<td>Faint</td>
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<tr>
<td>Shaky/Tremulous</td>
<td>Difficulty Speaking</td>
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<tr>
<td>Heart Pounding</td>
<td>Blurred Vision</td>
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<td>Nervous /Anxious / Irritable</td>
<td>Coma / Seizure</td>
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The older individual gives us a little more sophistication in being specific about hypoglycemia, or at least bringing it up above some of the other issues. And there are several types of responses that one sees with hypoglycemia. There’s the neurogenic responses in which there is the cholinergic responses of sweating and hunger and tingling. There are the adrenergic responses when the adrenalin or the epinephrine is secreted from the adrenal medulla. One sees the tremors. You see the pounding heart rate, the anxiety, the nervousness. But then there are the symptoms that are generated because the brain is not getting enough glucose to function properly, and those are the neuroglycopenic symptoms. Frequently patients complain of being weak, difficulty thinking, or confused to the observer. Faint, difficulty speaking, blurred vision, coma, and seizure are the ultimate outcomes of that. And this is the kind of thing one sees in our type I diabetic patient population. Much more common than you will see in any of the other conditions that we’ll talk about.
I want to review briefly some of the less common things that cause hypoglycemia, and there are some conditions of hypoglycemia that occur in the fed state. We traditionally talk about galactosemia and hereditary fructose intolerance. They cause hypoglycemia because they block hepatic glucose output because of the accumulation of phosphorylated input, or phosphorylated intermediates here. And so we’ve shut off the faucet. The drain’s still open. So the glucose level plummets.
A new group of disorders that over the last ten or fifteen years we’ve become increasingly aware of as significant problems with hypoglycemia is the defects in fatty acid oxidation. These are defects in which fatty acids cannot be transported or oxidized or ketone bodies cannot be formed. And since fatty acid oxidation drives gluconeogenesis, there’s a partial defect in gluconeogenesis. There are at least fifteen different enzymatic defects that are now known. There are no ketone bodies available to offset glucose utilization by brain. There is no fatty acid oxidation at muscle level so one has then increased the size of the drain and compromised the faucet input. So you have decreased glucose entry and increased glucose exit. These kids can present with profound hypoglycemia, blood sugars of 2, 3, 4, 5 mg/dl, and some will present with Reyes-like pictures. So it’s something for you to be on the alert for in that situation, as opposed to the child that presents with a seizure with a blood sugar of 32 or 35.
There is also a family of disorders of enzymatic defects in the gluconeogenic pathway. Again, I think it’s obvious that if you have a defect in glucose production or glucose release from glycogen that you would compromise the output of glucose. And in addition we know that since fatty acid oxidation is linked with gluconeogenesis, conversely gluconeogenesis is linked to fatty acid oxidation. And particularly in the patients with type I glycogen storage disease, they also have a functional defect in ketogenesis.
There’s the group of causes that are associated with growth hormone deficiency and cortisol deficiency, growth hormone plus cortisol deficiency, occasionally thyroid deficiency. And we have not a clue as to what the pathophysiology of that is, nor of ketotic hypoglycemia. And just as a warning, kids who are put NPO for long periods of time as young infants for surgery are also prone for hypoglycemia. I think that’s probably just related to fasting.
Then we come to probably the most common cause of hypoglycemia. That's hyperinsulinemic hypoglycemia. Whether it's caused by an endogenous defect in insulin secretion, or exogenous administration of insulin, the pathophysiology is very similar in which, when you have too much insulin, you increase glycogen storage. You block glucose release from the liver. You block fatty acid mobilization, so you decrease the substrate for ketogenesis. And you accelerate the rate of glucose utilization by muscle and by fat tissue. So once again, we've shut off the faucet. We've opened up the drain. Glucose concentrations fall. And in this situation there is no backup because there are very, very low ketone body concentrations. Which places the CNS at increased risk for neuroglycopenia and ultimately, with recurrent episodes, of permanent damage.
Establish the Diagnosis---
and Search for Etiology

- High Index of Suspicion
- Use a Reflectance Meter to Estimate Glucose
- OBTAIN THE CRITICAL SAMPLE BEFORE Rx:
  - Plasma glucose (gray top or on ice)
  - Insulin and C-peptide
  - FFA and β-hydroxybutyrate
  - Free and Total Carnitine, Acyl Carnitine
  - Cortisol and growth hormone
  - Consider a Glucagon Challenge (500 – 1000 µg)
- Plan Formal Evaluation -- when Critical Sample Results are available

So, to establish the diagnosis, you first have to think about it. I think any office practice should have a reflectance meter with some strips that are in some hermetically sealed strip containers. They’re real cheap. Your local representative will probably give you one so you can estimate the glucose if you’re there. If it’s an emergency room, the same thing. But you need to obtain the critical blood sample. That is, the sample at the time the patient presents with hypoglycemia. You miss an enormous opportunity to help with the diagnosis and the prevention of future episodes by doing that. And one or two more minutes of hypoglycemia is not going to make an outcome difference when in fact you’re going to have to go through several episodes to reestablish what the etiology might be. You obviously want to measure glucose by a method that is reliable, so you want a lab method. You’d like to measure insulin and C-peptides is co-secreted with insulin. In a situation in which a parent is giving insulin, the insulin will be very high and the C-peptide low, as opposed to a situation in which it’s endogenous insulin, in which both the C-peptide and insulin will be elevated. Obviously if you like to measure the fatty acids and the fatty acid oxidation defects, the fatty acids will be very high and the ketone bodies will be relatively low. Free and total carnitine and the acyl carnitines help us with those fatty acid oxidation defects. We’d obviously like to get growth hormone and cortisol for reasons that are not clear, but we always put them down, and occasionally it helps us. And if you’re thinking about it, you might think about a glucagon challenge test if you think the child has hyperinsulinemia. But that’s more of an elective fasting situation. These are the critical samples to obtain, and you don’t need to have all the slips filled out. Just get the blood done and set it aside, put it on ice, and make sure then it gets defined. And then, at the same time you have the IV in, you can bolus the child with glucose, not before. I can tell you hundreds of times that, “Oh, the child was hypoglycemic. We gave him the bolus and then we drew the samples.” “Well, hello. That didn’t help me at all.” If we have this data in hand, then we can formulate a plan. If we don’t have this data in hand, then we start all over again. We start with an elective fast and hope that we can stimulate a situation that might cause the recurrence of the hypoglycemia if we really think it’s a recurrent problem.
But, one kid that I want to spend a little bit of time on with you is the most common kid in your practices with hypoglycemia, and that’s the diabetic child. That individual has the highest risk of hypoglycemia for anybody that you have around.
The diabetes control and complication trial, which was focused on type I, proved that improved glycemic control reduced by 65% the incidence of microvascular disease in the retina. It also demonstrated that you reduce the incidence of neurologic outcomes. But that was at a cost. That was at a cost of nearly a threefold increase in severe hypoglycemia, defined as the individual being unable to deal with it themselves, requiring outside help. Not just seizures, but a threefold increase in severe hypoglycemia.
Now in this diabetic it is insulin-induced hypoglycemia. It is more frequent in type I’s than in type II’s, probably because there is more modulation of the glucose because the pancreas continues to make and be able to shut off insulin secretion in the type II except late in the disease course. In addition, the type I patient has a defect in primary counter-regulation to hypoglycemia. They cannot shut off insulin secretion as you might. If your blood sugar starts to fall, the first thing that happens, your beta cell shuts off, insulin secretion goes down, and it protects you. In addition, you will secrete glucagon that will raise your blood sugar back up. In the diabetic who is an insulin-requiring diabetic, a decrease in insulin cannot occur because they have subcutaneous depots and they are paralyzed in their ability to respond to glucagon.
If we do a controlled clamp – that is, we infuse a high dose of insulin and then infuse glucose to control it, you will notice that the first thing that happens in the normal individual is a decrease in insulin secretion, then an increase in glucagon and epinephrine as kind of regulatory hormone responses, then growth hormone, then cortisol. And finally you get down to a level where you start getting decreased cognition.
Now if you have recurrent episodes of hypoglycemia, whether it’s a normal individual or a type I diabetic, and you create hypoglycemia, you will start getting some symptoms of neuroglycopenia a little bit earlier in the diabetic than in the nondiabetic. Then you start getting autonomic responses. And finally you get the defects in cognition. With repeated episodes, these thresholds shift, such that your neuroglycopenic and autonomic responses get down very close to the cognitive response failure. This is your brittle diabetic. Doesn’t mean that they have brittle diabetes in the fact they can’t be controlled. This probably means that they are having recurrent and repeated episodes of severe hypoglycemia, sometimes in the middle of the night, that they don’t recognize. And this is called hypoglycemic unawareness, and it’s an extraordinarily dangerous situation. It is reversible. Get them from stopping, bouncing their blood sugars, and in fact this hypoglycemic awareness will return.
Diabetic Child

- Hypoglycemia is THE Limiting Factor in preventing long term microvascular complications of diabetes
- Good to Excellent Diabetic Control Results
  - 2 to 5 Mild Hypoglycemic episodes / week
  - 0.6 Severe Hypoglycemic episode / yr
- THE Most Common Cause of Hypoglycemia

So, in the diabetic child, hypoglycemia is the limiting factor for preventing the long-term microvascular complications of this devastating disease. We try to achieve excellent to good control. We drive the kids crazy. We drive the family crazy and we drive ourselves crazy to try to avoid those long-term problems. But in a good family, with a cooperative young person, we will have two to five mild episodes of hypoglycemia per week. And if we don’t get that kind of history, we know they aren’t taking care of themselves at all. We have a risk of about 0.6 severe hypoglycemic episodes per year per child under most circumstances. And for your practical purpose, it is the most common cause of hypoglycemia.
Objectives

- **Recognize**
  - Glucose Homeostasis is a dynamic system
  - Factors affect both Glucose Entry (Ra) and Disposal (Rd)

- **Understand**
  - Unique aspects of glucose homeostasis in Infants and Children
  - Pathophysiology of Hypoglycemic Conditions
  - Hypoglycemic Unawareness

- **Recognize**
  - The importance of the Critical Sample(s) in evaluating a child with hypoglycemia

So, hopefully, I have reviewed for you some of the dynamic aspects of glucose homeostasis and some of the factors that affect both glucose production and glucose utilization. And I hope you have a better understanding of some of the unique aspects of glucose homeostasis in infants and children, and the pathophysiology of at least some of the conditions, and made you aware of a condition called hypoglycemic unawareness. And I hope that you will all help me by getting that critical sample because it does help the evaluation.

Thank you very much.