The Orlando Sweater

70th ADA Scientific Meetings
Orlando, June 2010

The 70th Scientific Sessions of the American Diabetes Association were held in Orlando, Florida this year. Let me advise you that Orlando is not the place to be the last week in June. The humidity and the heat made it very uncomfortable for everyone. I watched several of my colleagues go off to Disney World and come back with very irritable and unhappy children and I was not envious whatsoever. I stayed in the air conditioned splendor of the convention center and rode the air conditioned bus back and forth. In our two mile jaunt we passed every national steakhouse chain in existence, three miniature golf courses and too numerous to count seafood shanties. The weather was so bad that I even passed up an opportunity to go to a baseball game. Those of you who know me know that that is a major statement.

Isn't Orlando supposed to be fun?

SL Tribune July 11, 2010

Glycohemoglobin Goals

The first session upon which I would like to report was the 8 a.m. Saturday session on A1c Targets in Pediatric Diabetes/Ideal Versus Real. Dr. Georgeanna Klingensmith from the Barbara Davis Center in Denver first reported what ADA considers to be appropriate targets for our patients:

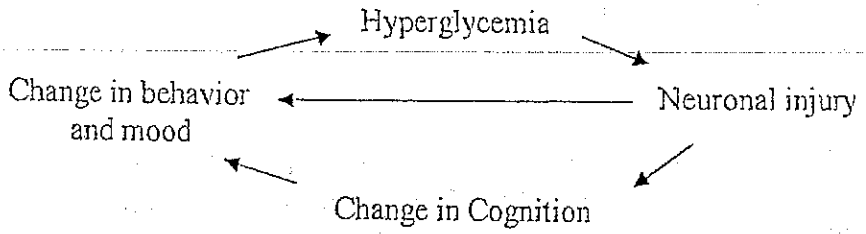
Age	Target A1c Levels
< 6 years	7.5-8.5%
6-12 years	< 8%
13-19 years	< 7.5%
20 years plus	< 7%

As far as blood sugars are concerned, fasting blood sugars should be somewhere between 90 and 180 mg% and post-prandial (after eating) blood sugars should be less than 180 mg%. She felt bedtime blood sugars were best between 120 and 180 mg%. She pointed out that the DCCT (the landmark study that was reported in 1994) achieved hemoglobin A1c values of approximately

7% in the adult category which then rose to 8% after the study was completed. The adolescents in the study had a hemoglobin A1c average of 8.6%. She then reported how various centers across the world are doing with their patients. The group from Hvidore had a mean hemoglobin A1c of 8.2%. The SEARCH patients have a mean of 8.3%. They felt that 44% of the children were in the good category, 39% were in the intermediate category and 17% were in the poor category. Whey looked at factors that were involved in the degree of control, they found the age of the patient, the duration of the diabetes, the presence or absence of insurance, the average household income, the frequency of blood testing, parental education, ethnicity and the type of insulin delivery all contributed to the degree of control. The pump patients had an average hemoglobin A1c of 8.0% whereas the multiple daily injection patients had an average hemoglobin A1c of 8.5%. Patients taking one or two injections per day had an average hemoglobin A1c of 8.6%. The Josslin Clinic in Boston had an average hemoglobin A1c in their children of 9% in the year 2000 and it had dropped down to 8.7% in the year 2005 due to a more intensive approach. We do not have more recent numbers from them. The Barbara Davis Center reported on 2,437 patients. Median hemoglobin A1c was 8.2% for children less than 6 years of age, 8.2% for children 6 to 12 years of age and 8.7% for children 12 to 18 years of age. Seventy-five percent of the patients who had a hemoglobin A1c of greater than 10% were teenagers. The Barbara Davis Center has done a program called "Know Your Number". They have found that 98% of their teens have been told what their hemoglobin A1c is and 60% could correctly state what their number was. They felt that there was much better control when the patient and the parent knew the goal and the result. She then raised the question if new technology would help the hemoglobin A1c success and mentioned the JDRF Sensor Study. These patients were given continuous glucose monitors and instructed to wear them consistently. The patients who were 25 years of age and older were able to drop their hemoglobin A1c by 0.4% with 80% of them using the sensor six days per week. The younger patients 15 to 25 years of age lowered their hemoglobin A1c by 0.1% but only 30% of them used the monitor six days per week. The youngest group, 8 to 14 years of age lowered their hemoglobin A1c by only 0.05% and 50% of them used it six days per week. Thus the newer technology is useful to a degree if it is used consistently. She concluded by pointing out that greater than 50% of our patients in the country are not meeting the ADA criteria. She felt we must modify our behavior if we are hoping to have better control. This approach will include intensifying the insulin, educating patients on five tests per day, educating the patients about hemoglobin A1c (including normal values, achieved values and the goals), and educating patients about glucose goals. She also pointed out that we need better sensors that are easier to use. In the discussion session, Dr. Guthrie from Kansas pointed out that we should be focusing on post-prandial (after meal) levels. He also pointed out that we should just not be counting carbs because protein is converted to glucose eventually. Dr. Dorothy Becker from Pittsburg stated that parents must have daily involvement with patients and with their records. Without that involvement the likelihood of good success drops considerably. *I reported on our hemoglobin A1c results a couple of years ago in this handout. Ours are very similar to what they are finding nationally although they may be slightly better. The average hemoglobin A1c seems to hover somewhere between 8.0 and 8.2%. We seem to have reached a floor below which it is hard to move. Our average hemoglobin A1c has been about the same now for about four or five years. Somehow we cannot quite get down into that 7.6 or 7.5% range that we would all like. I think Dr. Guthrie's point is well taken since we become so consumed with carbs that we forget fats and we forget protein. We need to recognize that they are an integral part of diet and glucose control. I cannot agree more strongly with*

what Dr. Becker said. As many of you know, I highly recommend refrigerator records and she is just stating that they are imperative. It is nice to know that some of the experts agree with me once in a while.

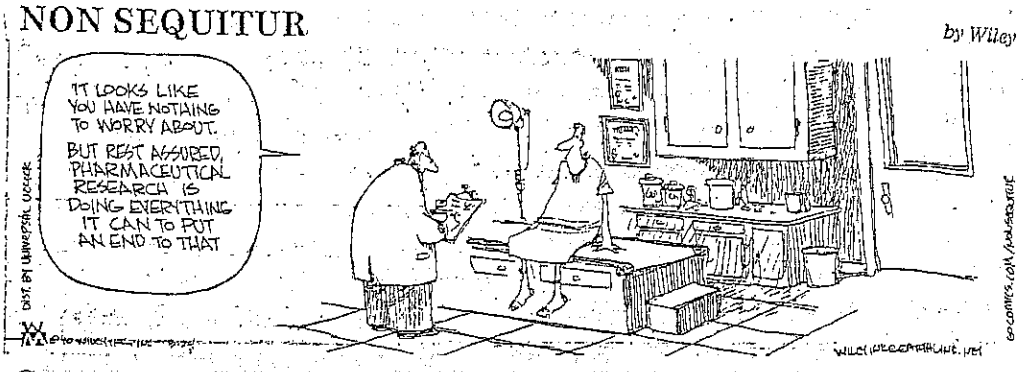
Dr. Timothy Jones gave a talk about barriers to achieving hemoglobin A1c targets and the risks of hypoglycemia. He pointed out that in the DCCT, the intensively controlled patients had significantly more episodes of severe hypoglycemia and that the adolescents had quite a few more than did the adults. Combining many studies, very tight control led to twelve severe hypoglycemic events per 100 patient's years. These included coma and convulsions. In his Western Australia group, he lowered the hemoglobin A1c from 10.5% in 1992 to 8.3% in 2001 but at the cost of tripling the severe hypoglycemic events. During the last six years, however, there has been a gradual decline in hypoglycemia and the average hemoglobin A1c is now 7.9%. He feels that the relationship of hypoglycemia and glycemic control that was reported in the DCCT in the 1990s no longer applies. We no longer see that relationship between good control and severe hypoglycemia secondary to new approaches, including better insulins (the rapid acting analogs, Lantus and Levemir), better monitoring and better patient education. He still sees the fear of hypoglycemia as the major barrier in achieving appropriate glycemic control. He pointed out that it is not just severe hypoglycemia that people worry about but even mild hypoglycemia occurring too frequently. The fear of hypoglycemia led to a decrease in quality of life leading to an increase in hemoglobin A1c. Interestingly, the increase in hemoglobin A1c secondary to the fear of hypoglycemia was not related to a history of past hypoglycemic events. Thus, it was a theoretical fear as much as an actual fear. As a result many parents give their children large snacks before bedtime leading to poor control. Parents who report that they oftentimes give a snack before bed had children with an average hemoglobin A1c of 8.3% while patients who report that they rarely or never give a nighttime snack had children with a hemoglobin A1c of 7.9%. Hypoglycemia can significantly affect the children also. They report that low blood sugars are unpleasant and can be embarrassing among their friends and classmates. Some have a fear of death and others worry about their loss of function at school. Finally many of them have the fear of the unknown. He felt that use of a continuous glucose monitor could reduce this fear of hypoglycemia. These devices would be particularly useful at times of increased risk: sleep, during times of impaired counter regulation and during and after exercise. He reported one study that showed that prolonged nighttime hypoglycemia is very common, occurring in 8.5% of the children studied. This hypoglycemia could be due to excessive insulin, a defect in the counter regulatory response by children at night or by late effect of exercise. Thirty-three percent of the children failed to respond to the hypoglycemia with counter regulation. He felt this was due to a blunted autonomic response. It can be reversed by avoiding hypoglycemia and can be reduced with the use of the continuous glucose monitoring. As far as exercise is concerned, even afternoon exercise can lead to a risk of late night hypoglycemia. *These points are why I frequently ask you to test your child at two or three in the morning if there has been significant exercise during the evening. The exercise can range from serious evening basketball games to simple night games with children running around the neighborhood. Again, continuous glucose monitoring sounds as though it might be very useful to avoid this problem.* Dr. Fergus Cameron then talked about hyperglycemia and its effect as a barrier to achieving target hemoglobin A1c levels. He first showed the following diagram:



He pointed out that presenting in diabetic ketoacidosis has already caused a hit to the brain because there is almost always some degree of sub-clinical cerebral edema. There is a lower gray cell density in the brain associated with both hyper- and hypoglycemia. A study that looked at patients over 10 years found that there was decreased brain volume and decreased brain gray matter in patients with hemoglobin A1c averages of greater than 9%. He reported on studies looking at changes in cognition (thinking). The acute affects of hyperglycemia showed a much reduced ability on the Wisc III which indicates decreased thinking ability. The study found that hyperglycemia had almost as much effect on decreased ability as hypoglycemia. Higher hemoglobin A1c values were associated with decreased cognitive ability in younger patients. When they were able to lower their hemoglobin A1c from 8.5% to 7.9% the patients performed significantly better. On top of that, glycemic variation (frequent highs and lows of blood sugars during the day) also has a significant impact on cognition. He pointed out that hyperglycemia also has a significant effect on behavior. It leads to irritability, short temper, mood swings, unreasonableness and aggressiveness. *As if you have not been told that before.* Studies have shown a significant improvement in behavior with improved control. They also show that improved control leads to better cognition and a better GPA. One study found that after ten years of diabetes, there was a good correlation between an increased rate of depression and an increased hemoglobin A1c level in adolescents. Still to be determined is what type effect glycemic memory has on the brain. He felt that hyperglycemia begets hyperglycemia via neurocognitive pathways. He pointed out that this has a definite effect on sports and driving. *Again I think you all have heard this in the past but maybe you will believe an international expert more than me.*

Finally Dr. William Clark from Virginia reported on Should We Assess Measures of Glycemia Other Than A1c in Pediatric Diabetes?. He pointed out that there can be lab to lab variability in A1c levels and that there can be mechanical bias in the levels. He also pointed out importantly that an A1c level is an average and does not reflect biological and glycemic variability. He felt that an A1c does not tell the whole story and does not demonstrate or reflect the glycemic variability that our patients have. He felt that possibly using fructose amine levels would be helpful because it at least demonstrates glucose control over the last three weeks only as opposed to the two and a half months that the A1c covers. He also felt that the Glycomark might be useful because it reflects the glycemia over days to weeks. It works best with a hemoglobin A1c level of 6-9%. He again emphasized that glycemic variability may contribute to short and long-term complications from diabetes. There are no studies that can prove this point yet but more and more the experts are feeling that variability in addition to the hemoglobin A1c average has the definite effect on long-term good health. The continuous glucose monitor system might be helpful here measuring the percent highs and the percent lows and helping us smooth things out. *As you have heard me say in the past, I would much prefer that your blood sugars and continuous monitor readings look more like boring Kansas than Colorado. There is*

good basis for smoothing things out as much as possible. I came away from this session feeling that our clinic is very similar to most centers across the country. We are all battling the same problems and coming up with about the same degree of success. In general, none of us are achieving what we would like to achieve. The newer insulins have allowed us to achieve much better control than in the past with less hypoglycemia. The newer technologic advances should help to some degree but really it all boils down to family involvement and family teamwork. Once again, we cannot succeed and your child cannot succeed without the continued involvement from your parents. Many of you should be highly complimented for the efforts that you make. Some should read this summary and recognize that there is still more work to do. I realize that managing diabetes is a tremendously stressful and time-consuming effort but all of these studies are showing how important and welcome your efforts really are.



Genetic Causes of Diabetes and Its Complications in Youth

I attended this session at 8 a.m. on Sunday (*I want you to notice that I was up every morning at the first session. This was not a picnic.*) The first session was about MODY, a type of genetic diabetes that has little implication for the standard patient so I will not discuss their presentation. Dr. Joseph Murray gave a nice talk on a new look at celiac disease. The question is if we should do genetic testing here. He pointed out that there are many common symptoms of celiac disease including skin rash, steatorrhea (oily stools), enamel defects in the teeth, aphthous ulcers in the mouth and delayed menarche (the onset of periods) in girls. As you know from earlier session handouts, celiac disease is an inflammatory state of the small intestine caused by a gluten intolerance. Gluten is a component in wheat and several other foods and causes an autoimmune response in patients with celiac disease. It is associated with other immune disorders besides diabetes. Patients with thyroiditis will have celiac disease about 3% of the time while about 5% of patients with Type I diabetes have celiac disease (other studies have shown it to be as high as 7 or 8%). There is also an association with Addison disease, Lupus erythematosus and Down syndrome. In the general population it occurs in 1%. He feels that celiac disease has become much more common over the last two decades and he does not think that it is just that we are looking for it more. Instead he feels that there has been a four to fivefold increase in prevalence since 1950. (*This increase is very similar to what we are seeing with Type I diabetes. I just wish we knew what was triggering these autoimmune phenomena in so many people.)* He feels that the tissue transglutaminase level is still the best form of detection. We measure a TTG in our patients every two years or so. He feels that if the TTG is positive, an EMA (endomysial antibody) is more sensitive and will help differentiate true celiac disease from false positives. He still feels that the intestinal biopsy is best diagnostic tool but he will treat if patients have both positive TTG and EMA levels. Patients with diabetes should be

followed sequentially but the majority who have celiac disease will be positive at the time of diagnosis of the diabetes. He went into genetic testing showing that some groups have as high a risk as 33%. Siblings have a risk of about 10% while the offspring of diabetics have a 5-10% chance of developing celiac disease. He also pointed out quite importantly that patients who do not know they have celiac disease and feel that they are asymptomatic in fact oftentimes have some symptoms. He listed abdominal pain, bloating, loose stools, arthralgias (joint pains), fatigue, frequent hypoglycemia and growth failure. *We need to remember that celiac disease may not show up with the classic symptoms and if you do notice these problems with your children, we should screen them for celiac disease. Celiac disease is not easy to manage and is considered just another hit by many of our patients but it is important that we know that they do or do not have it and that we treat it correctly if they do.* Dr. Andrzej Krolewski looked at genetic protection or predisposition for long-term complications in Type I diabetics. He pointed out that there is a 35% risk of proteinuria (protein in the urine) after 40 years duration of Type I diabetes and the risk of end-stage renal disease (renal failure) is about 20% at 40 years of duration. However the studies have shown that it is not just an accumulation of time and glucose levels but that there is definite susceptibility in some patients and insusceptibility in others. Proteinuria is more common in smokers and poorly controlled patients. There is a huge increase in proteinuria in patients who average an hemoglobin A1c of greater than 8.5%. But even patients with very good control can develop proteinuria at times. There are genes on four chromosomes (number 7, 9, 11 and 13) that can predispose to proteinuria with or without good control. The odds ratio increases from 1 to 1.4. Thus we need to monitor our patients carefully even when they are under tight control. *The genetic predisposition to diabetes and diabetic complications is in its infancy. We are going to find many more factors over the years. Eventually we will be able to pinpoint many patients who are at risk or not at risk for problems at the onset of their diabetes. Nevertheless, diabetic control remains the cardinal feature in preventing these problems.*

While we are talking about other problems associated with diabetes, I would like to report on two abstracts that were presented. First was an abstract looking at the prevalence of autoimmune thyroid disease and celiac disease in children and adolescents with Type I diabetes from Royal Oak, Michigan. They looked at 714 patients retrospectively. The patients were anywhere from 11 months to 9 years of age. Eight percent of the subjects had abnormal thyroid function with 49 cases of hypothyroidism and one case of hyperthyroidism. They found that the incidence of thyroid disease was greater in girls than in boys. The thyroid disease was diagnosed on average a little more than four years after the onset of diabetes. Seven percent of their patients had biopsy proven celiac disease with a slightly greater incidence in males than females. Again the celiac disease was diagnosed approximately four years after the onset of diabetes. I should point out that there are several studies looking at potential determinants of diabetes in children. The TEDDY study is a multinational epidemiologic study initiated by the NIH to identify environmental exposures triggering autoimmunity in Type I diabetes in children with an increased genetic risk for the diseases. They are not yet at a point where they can report back definite environmental risks but they did have two abstracts presented demonstrating their progress. These studies with genetically predisposed children may well help us understand eventually the causes of Type I diabetes. Until we know these triggers, we cannot, of course, prevent diabetes.

The Artificial Pancreas

Before I start talking about this session which occurred later in the day, I want to mention some rumors that some of my patients have heard. The artificial pancreas is not yet ready for use and will not be in the immediate future. I understand that it has been stated on the TV that it is about to be utilized but that simply is not true. This symposium was sponsored jointly by the ADA and the JDRF. The first speaker was Aaron Kowalski who discussed the topic: Are We Closer to Closing the Loop? He mentioned an in silico model of 300 virtual patients that has been ongoing (please remember virtual means not real). He states that the artificial pancreas is truly a evolutionary process. The first step is control to range, the second a nocturnal pump shutoff and third a multi-hormone release system. The first generation artificial pancreas is using the continuous glucose monitor systems that are currently available and current pumps. This system is not truly a closed loop since the pump is still controlled by the user. The second generation is being developed currently. It will use algorithms and will utilize advanced smart pumps and advanced continuous glucose monitoring systems. These systems are being finalized and have been utilized in hospital settings. They are not at a point where they can be utilized on an outpatient basis in a non-encumbering basis. The third generation will utilize dual chamber pumps that will provide both insulin and glucagon. The algorithms will be using multiple hormones and it will be a combined sensor and pump technology. Right now, we need faster insulins in order for this system to work properly. It may be that if we have a third chamber that contains amylin we might be able to utilize the current insulins. He warned that we must remember that this is still not physiologic because it is subcutaneous delivery. Dr. William Tamborlane discussed landmark continuous glucose management trials. He pointed out that we have better bolus dosing via these trials using the movement arrows, the alarms and using retrospective data. He reviewed a few evidence based studies. The Guard Control Trial used a combination of pumps and continuous monitors. There was a decrease in the hemoglobin A1c levels but he felt the control merely moved from very poor to poor. The Star One trials showed an improvement in hemoglobin A1c levels but not of statistical significance. (We will address the Star study a little later.) The JDRF trial was a twelve month trial with 338 patients. There were two arms to this study with some patients using continuous glucose monitoring while the other used the standard blood glucose monitoring. There was then crossover at six months. At baseline, the patients 7 to 14 years of age had an average hemoglobin A1c of 8.0%. The 15 to 24 year olds also had a hemoglobin A1c average of 8.0% and those older than 25 had a hemoglobin A1c average of 7.6%. After the six months, the older than 25 year olds had dropped their hemoglobin A1c by 0.5% but the less than 25 year olds had no change in their diabetic control. However, in the 8 to 14 year olds, only 42% of the patients wore the continuous glucose monitor consistently while only 34% of the 15 to 24 year olds wore the device consistently. Half the patients stopped using the continuous glucose monitor during the second six months. *I think the fact that only half were willing to go an additional six months shows some of the major problems with continuous glucose monitoring. If the patients will not wear them they really will not help very much.* The group that wore the sensor had less severe hypoglycemia but it was not statistically significant. In a secondary cohort study for the JDRF, 129 patients were evaluated with the continuous glucose monitor. Half of the patients were less than 25 years of age and they all had a hemoglobin A1c to start of less than 7.0%. At baseline, the patients averaged 91 minutes per day with a blood sugar less than 70 mg% and by 26 weeks use, the minutes had dropped to 68 minutes per day. When looking at more severe hypoglycemia, the patients at

baseline had a blood sugar of less than 60 mg% on average 40 minutes per day and at 26 weeks, the minutes had dropped to 18 minutes per day. The hemoglobin A1c was stationary with a baseline level of 6.4% and a 26 week level of 6.4%. Eighty-eight percent were less than 7.0% at completion. The rate of severe hypoglycemia was slightly better at 26 weeks but apparently not statistically significant. There was satisfaction with the use of continuous glucose monitoring in both the frequent and less frequent users. He also pointed out that Direct Net is doing a study in 4 to 9 year olds that has not yet been published.

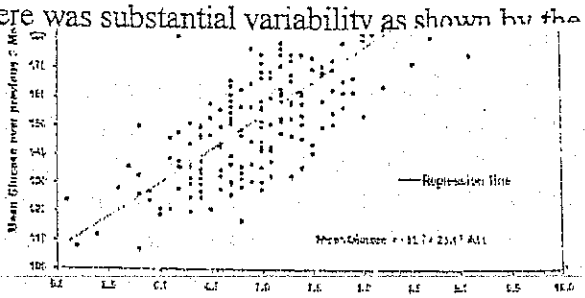
Dr. Merrilyn Ritholz discussed barriers to continuous glucose monitoring use. She said that using some of the standard psychosocial tests really did not predict who would do well with continuous glucose monitoring and who would not. Some retrospective studies showed that the patients who did best with continuous glucose monitoring were the ones who coped best with problems. They tended to respond using problem solving versus emotional decision making. They also tended to use the information for patterning as opposed to moment-to-moment decision making. Finally, for the older patients they found that spouses who encouraged the use of continuous glucose monitoring helped with the patients acceptance of it. Some of the problems with the use of continuous glucose monitoring included, 1) increased self-consciousness, 2) the feeling of being robotic, 3) that diabetes was always in their face in that they had constant awareness of their glucose numbers. They also found that in younger aged patients, the use of continuous glucose monitoring was less successful. She pointed out that we should use continuous glucose monitoring specific surveys to determine who might effectively use this technology. The patients will need significant patient education and counseling both in problem solving and in the coping with frustration. These patients had a hemoglobin A1c average of 8.5%. By the end of the study the patients were within the glucose target range 60% of the time. Only 2.1% of the time were they less than 70 mg% and 25% of the time were they above 140 mg%. *I really think continuous glucose monitoring will be of great help to our parents when they devise systems that patients will wear continually and they have worked out the various problems. It will be nice for our parents to finally be able to sleep at night without the fear of serious hypoglycemia.* At one of the last sessions on Tuesday, Dr. Bergenthall presented the Star III data at the late break news session. This was a study looking at the use of continuous glucose monitoring in patients with pumps or multiple daily injections. There were 485 patients who were followed for one year. The age ranged from 7 to 70 years. They were not in particularly good control with a hemoglobin A1c average of 8.3% for both groups. The hemoglobin A1c ranged from 7.4 to 9.5% at baseline. They were followed every three months and at 12 months the patients using pump and continuous glucose monitoring had an average hemoglobin A1c of 7.5% versus the 8.1% for patients on shots. In the adult population the difference was 7.3% versus 7.9% and in the pediatric age group the patients on pump and monitor had an average hemoglobin A1c of 7.9% while the patients with continuous monitoring and multiple daily injections had an average hemoglobin A1c of 8.5%. They also broke it down by the amount of time spent with the sensor:

Hemoglobin A1c Values

% Sensor Use	Pumps	MDI
0-20	7.5%	8.0%
21-40	8.0%	8.2%
41-60	7.7%	8.4%
61-80	7.5%	8.2%
81-100	7.3%	8.3%

Again we see definite improvement but not as much as we would like to see. A drop from 8.3% hemoglobin A1c to 7.9% is not as useful as we would like to see. Obviously there is much more for us to learn. They found no significant difference between the pump and shot users in terms of hypoglycemia. They felt in summary that the use of the pump and continuous monitoring led to a significant decrease in hemoglobin A1c in all age groups. Its use was not associated with increased hypoglycemia or ketoacidosis.

There were several abstracts that were presented on the use of continuous glucose monitors. Dr. Darrell Wilson from Stanford presented the JDRF continuous glucose monitoring data, comparing hemoglobin A1c and mean glucose. They used 199 patients who used near continuous glucose sensor data (greater than or equal to four days per week) for three months. They then compared the average blood sugars levels with the achieved hemoglobin A1c level. They found that there was relatively good agreement between the average blood sugar and the hemoglobin A1c but there was substantial variability as shown by the graph below.



They concluded that estimated mean glucose values based on hemoglobin A1c values should be used with caution. A group from Germany looked at the accuracy of continuous glucose monitoring systems. They compared the monitor's levels versus the levels they obtained while the patient was in the hospital. Thus they were not using meters as comparison. They found the mean absolute deviation was 24.5 plus or minus 24.0 mg/dL. Ninety-three percent of the readings were in zones A and B of the Clark Error grid but 6.4% were in zone D. Zone A is considered to be good accuracy and only 67.4% were within that range. They concluded "thus, while continuous glucose monitoring systems had high specificity (97%) and good negative predictive value (95%) for hypoglycemia positive predictive values (42%) and sensitivity (30%) were poor. In conclusion further improvements in the accuracy of continuous glucose monitoring system measurements seem to be necessary in particular for a more reliable detection of hypoglycemic episodes." *This merely means that the monitors are still not at all as accurate as we would like for primary use. Remember the manufacturers do not claim that these devices should be used as the sole means of determining blood sugar levels. They feel that their devices are still only additional information to the blood glucose monitoring that our patients do. Most*

of our patients, however, seem to forget this fact and want to use it as their only means of glucose determination. Another problem that we have with the continuous monitors is that there is a lag between the monitor and blood glucose meter since the monitor is measuring interstitial fluid and the meter is measuring blood glucose. A group from Australia looked at the Medtronic Guardian continuous glucose monitoring system and found that the intrinsic lag time was anywhere from 8.3 to 40 minutes. They felt that this was contributing to the mismatch between continuous glucose monitoring readings and blood glucose concentrations. *Once again we cannot rely on the current generation of continuous glucose monitor systems to provide all the information we need. We need to look at the movement arrows rather than the absolute numbers much of the time. They will enable us to anticipate problems but the absolute numbers may be a fair degree off from what you would obtain with you meter.* A group from Atlanta reviewed the published literature on continuous glucose monitoring use. They eventually were able to evaluate studies that included 1,505 patients with a mean age of 27.73 years. They found the use of continuous glucose monitoring both in randomized trials and retrospective studies resulted in better metabolic control than patients who used blood glucose monitoring alone. There was also a significant short and long-term reduction in hemoglobin A1c levels and lower rates and duration of hypoglycemia and hyperglycemia. I have included the following chart and I realize it is a little confusing.

Outcome	All CGM vs. SMBG	RT CGM vs. SMBG	Retrospective CGM vs. SMBG
A1C % Δ baseline to 4-8 wks	-4.6579*	-4.6579*	N/A
A1C % Δ baseline to 12-16 wks	-8.3549*	-9.2800*	-4.6150*
A1C % Δ baseline to 24-26 wks	-2.7055*	-2.7055*	N/A
Duration BG ≤ 55 mg/dl (min/day)	-4.3233*	-9.3412*	-9.3412*
Duration BG ≤ 80 mg/dl (min/day)	-11.3328*	-10.3612*	-10.3612‡
Duration BG 71-180 mg/dl (min/day)	59.4700*	69.7840*	69.7840‡
Duration BG ≥ 240 mg/dl (min/day)	-49.2582*	-49.2582*	N/A
Hypoglycemic events/day (BG <70 mg/dl)	0.1414*	0.0	0.3468†

Of interest was that if we look at all the continuous glucose monitoring patients combined in the first column, the hemoglobin A1c dropped 4.6% at 8 weeks of use, dropped 8.3% at 16 weeks use but then dropped only 2.7% at 26 weeks. The rest of the columns are fairly self-explanatory looking at the number of minutes per day that the patients were less than 55 mg% and less than 80 mg%. They also looked at the duration of blood sugar greater than 240 mg%. *These studies show that in older patients, the continuous glucose monitoring certainly does seem to have some beneficial effect. These results have not yet been translated to the pediatric population but hopefully that will be done in the near future.* Satish Garg and his group from the Barbara Davis Center looked at the effect of continuous glucose monitoring in patients using pump or multiple daily injections. His results were a little different from what I reported earlier. In this group, there was a significant drop in hemoglobin A1c in both the pump (CSII) and shots (MDI) patients. You can see the results on the graph:

	CSII	MDI	P-value*
Per protocol analysis population (n)	17	17	--
End of blinded period: 4-wk A1c (%)	7.77 (0.66)	7.72 (0.53)	0.77
8-wk A1c (%)	7.46 (0.61)	7.65 (0.68)	0.27
12-wk A1c (%)	7.18 (0.45)	7.36 (0.68)	0.26
16-wk A1c (%)	7.28 (0.55)	7.52 (0.68)	0.21
20-wk A1c (%)	7.24 (0.59)	7.38 (0.64)	0.32
24-wk A1c (%)	7.39 (0.64)	7.56 (0.72)	0.30
Unblinded-Blinded time spent <70 mg/dl (hr/day)	-0.52 (1.02)	-0.45 (0.92)	0.83
Unblinded-Blinded time spent 70-180 mg/dl (hr/day)	2.55 (2.07)	1.41 (2.07)	0.12
Unblinded-Blinded time spent >180 mg/dl (hr/day)	-2.03 (2.51)	-0.96 (2.46)	0.22

*independent t-test

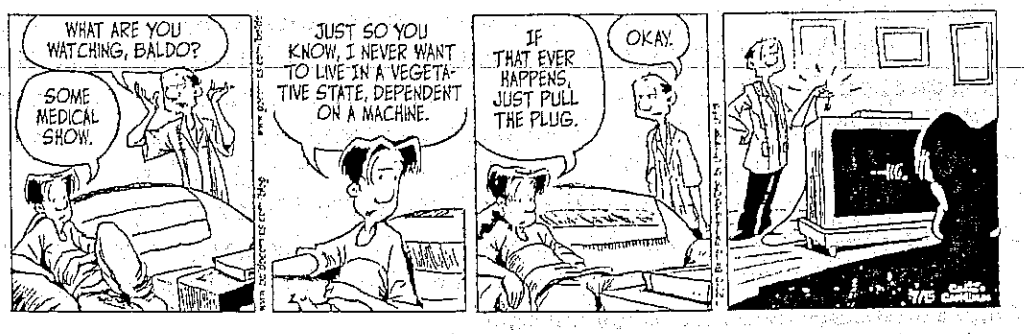
The same group from Australia looked at altering the low alarm on the continuous glucose monitoring monitor during exercise. They reported that when blood glucose levels are falling

rapidly, continuous glucose monitoring systems tend to systematically overestimate blood glucose levels, particularly in the low glucose range. They raised the level at which the monitor would sound an alarm from 72 mg/dL to 99 mg/dL during exercise and found that they could reduce the false alarm rate considerably. Thus they recommend that our patients when exercising increase the level to 99 mg/dL. *I was interested that they found that the continuous glucose monitoring system overestimated the blood glucose level by an average of up to 50 mg/dL during exercise. I had no idea that this was a problem.* The group from Josslin Clinic looked at barriers and benefits to children, parents and adults using continuous glucose monitoring. The results are on the following chart:

	Adults (%)	Youth (%)	Youth Parents (%)
What is the best thing about this device?			
Trends/Graphs	53	43	50
Ability to self-correct	43	25	28
Available CGM data	28	26	29
Detect low BG	17	32	27

What is the worst thing about this device?			
Alarms	34	34	16
Body issues	26	24	35
Pain at insertion	12	26	31

They found that "parents of frequent CGM (greater than or equal to six days per week) users were more likely to report the benefit of using CGM data to improve T1D care (42%) than parents of less frequent users (21%)". They also pointed out that parents of patients who used the CGM less frequently reported more body issues (39%) as a barrier compared with the parents of more frequent users (29%). They concluded "the lack of sustained CGM use by younger participants may be due in part to reported barriers, particularly the frequency of alarms, body issues and pain. Interventions that tailor CGM training programs to proactively address common barriers and promote positive attributes may improve successful implementation of CGM across the age span of persons with Type I diabetes. *These kinds of studies will be very useful in helping us try to sort out who will be successful with continuous glucose monitoring and who will not.* Finally a group from Portland looked at the use of infusing both insulin and glucagon in a closed loop system. There were thirteen adult subjects studied and they each wore two continuous glucose monitors and two pumps, one providing insulin and the other providing glucagon. They also had a group doing the same but instead of glucagon had a placebo. The glucagon plus insulin delivery, when compared to placebo and insulin, significantly reduced the duration of hypoglycemia of blood sugar levels less than 70 mg/dL (15 plus or minus 6 versus 40 plus or minus 10 minutes per day). They concluded "automated glucagon delivery markedly decreases hypoglycemia during closed loop glycemic control. Glucagon may fail to prevent hypoglycemia when insulin effect is high or when glucagon delivery is delayed due to sensor bias." *This again takes us back to the idea of multiple hormone infusion via closed loop systems. These are the first steps that will be taken to ultimately give us a closed loop system that probably infuses insulin, glucagon and amylin so that we can have less worries about hypoglycemia and faster response times. This is a fascinating area of research but we still have a long way to go.*



New Insulins

Also on Sunday (you can see I was very busy this day) I went to a seminar on Newer Insulins-As They Approach Availability What Should We Know About Them? First to speak was Dr. Michael Weiss on warp speed insulins. He pointed out that we have a basic problem with our fast acting insulins: they are too slow to mimic the first phase onset of insulin in non-diabetic patients and they also have a tail that leads to lower blood sugars a few hours out, causing more snacking. The goals he felt should be, 1) an insulin that better mimics normal insulin release, 2) an insulin that reduces the risk of late hypoglycemia, 3) an insulin that has better efficacy in pumps and 4) an insulin with less variability. He says that the basic problems lie in physical degradation of insulin in the vials and in pumps and poor absorption kinetics. One approach is to use a halozyme (hyaluronidase) to modify the absorption site. This leads to better diffusion and more rapid absorption. Various companies are working with the use of hyaluronidase. VIAject insulin is zinc free and is much more rapid than the current analogs, NovoLog and Humalog. However the problem is that first it is formulated as a powder and must be dissolved by the patient and is thus a two step process (one of the VIAject reps claims that you do not need to reconstitute so I am not quite sure who to believe at the moment) and it has a four to six hour tail which would not relieve the problem of late hypoglycemia. Another approach is to create non-standard side chain changes. The current insulins, Humalog, NovoLog, Apidra all have b-chain beta strand alterations. The question is if a change in the beta chain could lead to more rapid disassembly and yet still be stable. He was wondering if halogenation could alter the electrostatic properties leading the insulin to be monomeric, have native potency, have enhanced stability and decrease binding to IGF-1 receptors. This insulin would be much faster than Lispro. Another alternative is to develop an ultra-stable single chain insulin monomer. This would allow delivery of insulin without zinc extraction or enzyme degradation. These insulins are still in production and will not be available for a few years but promise some hope. *We have been fighting this problem for the last few years as we realize that the timing it has again become critical with our rapid acting insulin. They certainly work much faster than the old regular but not as rapidly as we had hoped. Maybe some of these newer insulins will allow us to no longer have to worry about timing between injections and eating.*

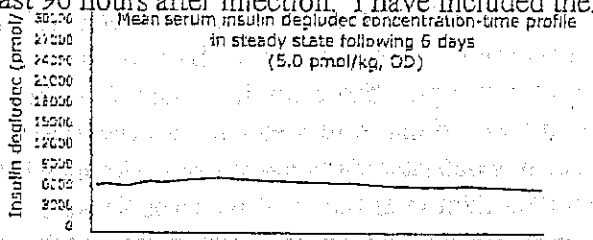
Satish Garg talked about slow release insulins. He pointed out that our two long acting drugs right now are not quite what they ought to be. He felt Levemir was definitely a twice per day insulin and that Lantus not infrequently required two shots per day. He mentioned the new insulin degludec. In this instance the threanine is removed from the beta chain which leads to multiple hexamers and this leads to longer duration and less variation than is found with Lantus.

In one study of 177 patients with Type I diabetes, the use of Degludec led to no change in hemoglobin A1c compared to Lantus but led to decreased fasting glucose levels. There was less hypoglycemia and less nocturnal hypoglycemia and more patients reached the goal hemoglobin A1c even though the overall average did not change. Lilly is also working on a new basal insulin and there is work going on with patch pumps that would provide a basal insulin through the day at a steady level.

Dr. William Cefalu talked about alternate delivery methods. He reviewed nasal insulin and noted that it was first proposed in the 1930s. The problem is that it causes quite a bit of nasal irritation and has low bioavailability. When it was tried in 1995 it produced worsening A1c levels and was not released to the public. A new insulin named Nasulin is a recombinant insulin with an enhancer. It is absorbed rapidly and peaks at about fifteen minutes (this is much quicker than the subcutaneous insulins). In a three month study in diabetics, the hemoglobin A1c was reduced by 0.5%. They are looking to outsource it so that it can be produced commercially. We do not know quite when that will occur. Viatab is a sublingual insulin and he states there are no clinical studies yet. Oralyn is a buccal insulin that produces about one unit of insulin per puff on the inside cheek. There have been some studies in Type II diabetics where it was found it had more rapid absorption than the subcutaneous insulins. There have been a few small studies that showed that it was equally as effective as injectable insulin. They have had some phase 3 studies but the data is not yet out. We also have oral insulin but the problem is that there is marked degradation as the insulin passes through the stomach into the intestine. There are five different companies working on oral insulin at the moment. It does not sound like this will be out any time soon for Type I diabetes. Finally he reviewed inhaled insulin. As you remember, Pfizer released Exubera a few years ago but took it off the market when it was found that most Type II patients were not at all eager to use it because it was so cumbersome. There also were some significant lung changes that developed. MannKind is the only company proceeding with inhaled insulin. Their technosphere has ultrafast uptake. In a one year study the hemoglobin A1c results were equal to those with multiple daily injections. They also claim that it attenuated weight gain and caused less hypoglycemia. There was some slight reduction of FEV_1 which is a measurement of lung capacity. The patients also developed antibodies to the insulin but at this point they are not felt to be deleterious. *Thus I can assure you that people are still working on alternatives to insulin injections. Most of them will not pan out as we have discovered in the past but perhaps one of them will. Stay tuned and we will see what happens over the next few years.*

There were several abstracts presented about new insulins. One was from Germany looking at VIAject versus regular insulin in Type II diabetes. *I have no idea why they insist on comparing their new insulin to regular insulin since we have not used it for years. Of much greater importance is how it compares to the analogs that we currently use.* They found that the final hemoglobin A1c changes were similar between the two groups. Non-severe hypoglycemic events were significantly reduced in patients using VIAject. They made no mention of severe hypoglycemic events. Patients treated with VIAject gained significantly less weight than those treated with regular insulin. There were more injection site reactions (pain or irritation) in the VIAject group but this declined during the course of the study. *This study was done with Type II diabetics and I am not quite sure what it was meant to accomplish. I guess it shows that VIAject is as good as regular insulin but what we really want are the later studies versus the analogs.*

Then there was a study from Norway looking at insulin degludec which they reported as a novel insulin analog that forms soluble multi-hexamer assemblies after subcutaneous injection resulting in ultra-long duration of action. Again these patients were Type II diabetics and the study was done in comparison with insulin glargine (Lantus). The study reported no severe hypoglycemic events. Rates of confirmed hypoglycemia (glucose less than 56 mg/dL) were lower for the patients on insulin degludec. They reported also that very few confirmed nocturnal hypoglycemic events were reported. They state "in conclusion, this proof of concept trial showed once daily insulin degludec to be safe, well-tolerated and effective. Insulin degludec provided comparable overall glycemic control to Lantus at similar rates of hypoglycemia, but with the additional benefit of post-dinner glucose control." *Again this is an early study in patients that are of little similarity to our own. Nevertheless the insulin is slowly coming out and being used in clinical trials.* Another study from Denmark also looked at insulin degludec. They were looking at mean serum insulin concentrations. I will not go through all that they found other than the fact that the steady state pharmacokinetic profile indicates a smooth and stable exposure over 24 hours. They said that insulin degludec has a half life of longer than 24 hours and is detectable in the circulation for at least 96 hours after injection. I have included their graph to show how steady the insulin is:



A study from Princeton looked at the use of Nasulin versus Lispro. They found that Nasulin demonstrated a significantly more rapid onset of action than Lispro (Humalog). This difference resulted in a pharmacodynamic response optimally timed to occur in the first hour following the meal in the Nasulin group with a smaller counter regulatory glucagon response later. They concluded that Nasulin has the potential to offer effective glucose lowering immediately following the meal with less risk of hypoglycemia (later). *If we could dose nasal insulin effectively, this might solve some of our problems with delayed onset of rapid acting insulin.* Finally there was also a poster presented on oral insulin. I am not going to go through their results since they are very preliminary. They did find that it was absorbed in 61% of the instances somewhere between 40 and 180 minutes of administration. Beyond that, I do not think they presented any particularly interesting data. *Thus people are still working on alternatives. Some of the other meetings I have gone to over the past few years gave me the impression that companies were pretty much giving up on alternative insulin delivery. It appears that they are still present if not thriving.*

ZITS

by Scott & Borgman

On Monday I attended a session looking at the changes in pediatric diabetes. First to speak was Anette-Gabriele Ziegler addressing the escalating incidence of Type I diabetes in youth. She pointed out that Type I diabetes is rising worldwide. There is a good deal of variability throughout the world but just about anywhere you look the incidence of diabetes is going up. The highest rise is in Romania and Poland interestingly. Overall there seems to be a 3.9% increase per year. The highest increase is in children less than 4 years of age. As a result, there is no longer a pubertal peak of new onset but a plateau pretty much throughout childhood. They also have found that there is a moderate increase in the number of patients developing Type I diabetes older than 20 years of age. *We have definitely seen this rise at our facility. We seem to be setting new records each year and not infrequently records that were considerably beyond the previous records. Likewise, we have been commenting for about the last three years at how many very young children are developing diabetes. It used to be that we rarely saw a child under 2 with new onset diabetes and now we are averaging two or three per month.* She questioned if it was due to earlier initiation of the auto antibodies that cause Type I diabetes or if it might be more rapid progression. She compared the results from BABYDIAB from 1989 through 2000 versus TEDDY from 2003 to 2010. She states that the appearance of auto antibodies was identical between the two groups. However the progression was much faster in the TEDDY cohort even when the genetics were similar. The rate of anti-GAD antibody was earlier and more rapid in TEDDY and the children in TEDDY achieved multiple antibodies faster than the earlier children in BABYDIAB. She also noted that the gene types in Type I diabetes are changing. She states that this implies that there are different and more pathogenic causes of autoimmune diabetes than we recognized. She looked at some of the environmental factors that may play in these changes. She felt that obesity really does not seem to explain the increase although the DPT1 study that our patients were involved in about ten years ago does show some effect. There have been studies showing that early introduction of foods may have an effect. In particular she mentioned fruits and berries before 3 ½ months of age, cereal before 3 months of age and gluten before 3 months of age. The DAISY study indicated the cereal while the BABYDIAB indicated the gluten. She stated that the maternal hemoglobin A1c may play a slight role in that if the maternal level is slightly higher it may be protective until at least 6 ½ years of age for the child. Therefore the fetal and early infancy environment may have a definite effect on the development of diabetes later. There still is a question about early vitamin D supplementation as being protective. In a German study this was not seen but in several others vitamin D has become a very popular subject.

Dr. Ralph D'Agostino talked about clusters of increased cases of Type I diabetes. He felt that the data to this point is inconclusive but there might possibly be clusters. He used the SEARCH data of 5,800 cases diagnosed between 2002 and 2006. He found that the cases were somewhat temporal in that more were diagnosed during the winter months which were more apparent in areas that had a true winter. There was a temporal relationship based on the month of birth with children born between May and June having the highest rate of diabetes whereas the children born from November to February had the lowest rate. He questioned if this was related to vitamin D production from the sun by mothers in the summer. He did not see a spatial relationship in the study since the rates were what would be expected in each area. His point is that diabetes should be made a reportable disease and there should be registries over large population bases. It is through such data that we can truly see relationships. Dr. Rebecca Lipton

talked about the changing natural history of microvascular complications in childhood onset Type I diabetes. She pointed out that children with diabetes have a three times greater risk of hospitalization and that in her area of Chicago there is a 2.7% increase in incidence of diabetes in the 1990s. Her question was if the burden of complications was also increasing. The Pittsburg group reported a decreased incidence of retinopathy, nephropathy and neuropathy over the past 25 years. Australia reported a significantly lower rate of retinopathy and neuropathy in patients diagnosed in 2001 versus patients diagnosed in 1994. On the other hand, they did have an increase of peripheral nerve abnormalities. End stage renal disease has decreased since 1990 in children less than 20 years of age. She felt that greater fluctuations in the hemoglobin A1c (a high level followed by a lower level then followed by a higher level etc.) help predict both retinopathy and nephropathy. This was particularly the case in patients with higher average levels of hemoglobin A1c. Short-term fluctuations, however, were not predictive. *I am not at all surprised at the decreased rate of retinopathy and nephropathy that she reported. In our practice, we see much less eye disease than we use to. I remember back in the late 1980s when many of our late teenagers would have retinopathy requiring laser therapy. I can think of only one patient in my group now that has any sign of retinopathy. Likewise the rate of renal disease has decreased tremendously. We are startled when we have an abnormal albumin creatinine ratio since it is so less common. I have attributed it to our more intensive approach using basal bolus insulin. We have seen this change both in patients on pumps and multiple daily injections. Nevertheless we must remain on our guard because we fully expect our patients and children to live many more decades and we do not want complications to occur later on.*

From Children to Adults

I also attended a symposium on Monday addressing this issue. There was a great deal of discussion and I can only report a small amount. Dr. Howard Wolpert reported on identifying the unique needs of transition care for young adults with Type I diabetes. He pointed out that the main problem is that young adults pay little attention to self care. He illustrated this point with the EDIC study which was the follow-up of the DCCT study mentioned earlier. The adolescents in the DCCT actually had a higher hemoglobin A1c twelve years later than they did during the study. These patients now were 26 and 27 years old. He pointed out that diabetes has a two times increased mortality in young adults. He felt the risk factors for death could be explained by several problems. There were the acute deaths: there was a 4.4 times greater risk when patients were living alone, a 4.6 times greater risk when the patient was abusing drugs and a 4.6 times greater risk if the patient had psychiatric disorders. He felt that substance abuse had about a 10 to 25% prevalence rate in young adults with diabetes. Cocaine and amphetamines particularly were abused and led to a greater risk of ketoacidosis. *I am appalled at this rate that*

he quoted. In my experience cocaine and heroin certainly are right up at the top but so are the methamphetamines. Eating disorders when untreated led to a very high rate of retinal and kidney changes. Patients with eating disorders on average had a hemoglobin A1c of 9.6% and 86% showed retinal changes and 43% showed albumin in their urine. He also pointed out in young women with Type I diabetes, 30% purposefully omit insulin for weight loss. After eleven years, their risk of death was 3.2 times greater than in the general population. He felt adulthood should be defined by three characteristics: 1) responsibility for self-care, 2) independent decision making and 3) financial independence. He felt that in most cases this will occur by the age of 29 years. He felt that the college years had certain barriers to self-care. He very much included diet in this category along with an increased sense of responsibility and a very irregular schedule. He discussed when a patient should transfer to adult care. He felt that if a patient was having a difficult adjustment to college or work and had a strong bond with the pediatric team, the transfer should be delayed perhaps for several years. He felt that the demands of the early young adult years led to significant distraction particularly if there were new physicians and new diabetic plans. Dr. Denis Daneman from Toronto discussed Moving On-Facts and Figures About the Transition to Adult Care. He pointed out that the transition is truly from family centered care to self-management. It was also a period changing from surveillance to treatment of complications. He felt that the transition should occur when there is evidence of self-care and responsibility versus a specific age. He pointed out, as many others have pointed out, that this is a transition in process rather than an event. He stated that the patients are much more likely to be hospitalized in ketoacidosis if there is a complete shift of team (both physician and educator) and thus the transition needs to be gradual rather than an abrupt event. He did criticize pediatricians (*and I suspect me in particular*) for never being willing to let our kids get away. He concluded by saying that there is a growing consensus that the new 18-year-old is truly the 28-year-old. With this he meant that instead of emancipation at 18 the diabetic has emancipation closer to 28 years of age. *Obviously this is an ongoing debate that will not be resolved for many years. In talking to my friends at the Barbara Davis Center and several other clinics across the country, they prefer to keep their patients through college as long as the facilities can handle the number. That is the big problem at our clinic because we simply do not have the space. Thus we are obliged to move patients on a little earlier than many of us would like.*

Abstract Presentations

Next I would like to go through a variety of abstracts and posters that were presented at the meetings. There is no rhyme or reason as to their order so do not try to find any good structure here. First I wanted to report on a poster comparing the new One-Touch Delica lancing device. This is not news now since many of you have started receiving this device but some may not be aware of it. It "contains features to reduce lancing pain, including improved lancet control and stability, reduced vibration and 33-gauge lancet". They compared fingertip pain scores with many of the other current clickers. The results are on the chart following:

Comparison	Median Pain Scores (mm)	IQR (mm)	Significance Level
Delica Comfort	18.0 56.5	48.8 54.3	p<0.0001
Delica Multiclix	30.5 45.0	62.3 61.4	p<0.05
Delica Microlet2	29.3 72.3	60.4 43.4	p<0.0001
Delica Softclix	26.8 31.0	61.4 64.4	p=0.24 (NS)

They concluded that Delica was either less painful or no different than the comparison devices. *I think our patients would agree that his is a major step forward in blood glucose monitoring.* Another study from Great Britain looked at a comparison of NovoLog and Apidra in pump use, looking particularly at occlusion rates. They found that the overall rate of occlusion in insulin infusion catheters could be slightly higher with Apidra but earlier occlusions may be more likely to be seen with NovoLog. *I need to emphasize that these differences were not significant. My take-home message is that either insulin is probably perfectly acceptable for pump use. This study did not look at Humalog but I suspect they would have found the same result had they tested Humalog versus Apidra.* A study from the Barbara Davis Center looked at adolescent females with Type I diabetes and physical inactivity. They questioned 228 girls between the ages of 11 and 24 years of age as to their degree of physical activity. As can be seen from the table, girls who were 16 to 19 years of age reported significantly fewer physically active days in the last week and in a typical week than girls who were 11 to 15 years of age. They found that adolescent females with Type I diabetes report exercising for at least sixty minutes about three times per week which does not come close to reaching the international recommendations of sixty minutes of moderate to vigorous activity per day. They concluded "it is particularly important that adolescent girls with Type I diabetes be encouraged to exercise, since more frequent physical activity is associated with better glycemic control". *Do not say that you have not been told this in the past. We harp and harp on the need for activity but it still is not being done. I am not just whispering in the wind when I complain that patients are simply not getting the activity that they need and it is having a negative impact on their control. This study reminds me of the one from last year where they found that 18-year-old girls did 15% of the typical activity of an 8-year-old girl. Somehow we need to incorporate exercise into our diabetic regimen much more effectively than we are currently doing.*

	All Participants (N=228)	Ages 11-15 years (n=97)	Ages 16-19 Years (n=116)	Ages 20-24 years (n=15)
Age at visit (years)	15.9 ± 3.0	13.5 ± 2.7	17.1 ± 1.0 [a,b]	21.4 ± 1.6 [a,c]
Duration of diabetes (years)	6.7 ± 4.9	5.0 ± 4.6	7.4 ± 4.4 [a,b]	12.6 ± 4.3 [a,c]
A1c (%)	9.3 ± 1.9	9.3 ± 1.9	9.2 ± 1.9	9.5 ± 2.0
Insulin dose (units/kg body weight/day)	0.97 ± 0.34	1.04 ± 0.34	0.92 ± 0.34 [a]	0.89 ± 0.24
BMI (kg/m²)	23.8 ± 5.1	22 ± 3.6	25.0 ± 6.0 [a]	24.8 ± 3.3
BMI z score	0.70 ± 0.75	0.48 ± 0.84	0.84 ± 0.82	0.39 ± 0.77
Blood Pressure				
Systolic (mm Hg)	112 ± 14	109 ± 8	114 ± 10 [a]	115 ± 10
Diastolic (mm Hg)	66 ± 9	64 ± 8	68 ± 10	68 ± 10
Pulse	84.0 ± 13.4	84 ± 12.2	83 ± 13.7	92.3 ± 16.6 [b,c]
Total Physical activity (number of days over the last week that the subject was physically active for at least 60 minutes per day)	2.7 ± 2.3	3.0 ± 2.2	2.3 ± 2.24 [a]	2.7 ± 2.1
Typical Physical activity (in a typical week the number of days that they are physically active for at least 60 minutes per day)	3.1 ± 2.2	3.6 ± 2.1	2.7 ± 2.2 [a]	3.5 ± 2.4
Met physical activity guidelines (%[n])	5 (12)			

Another study from Denver looked at the age of onset of menstruation in teenage girls with diabetes. They found that the age at menarche (the first menstrual period) was later in girls with Type I diabetes diagnosed prior to menarche than for girls diagnosed after menarche and that the girls who developed diabetes prior to menarche were significantly later than the average non-diabetic girl. Interestingly, menarche age was not associated with hemoglobin A1c levels. They also found that 34.3% of the girls with diabetes had irregular menses. They concluded that "despite improved treatment in recent decades, menarche delay and high prevalence of menstrual irregularity is still observed among girls with Type I diabetes". *I included this study in this report merely to lend reassurance to girls who are late with menarche and who have irregular*

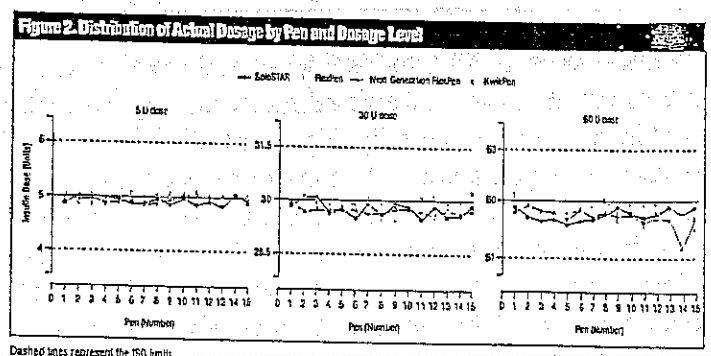
menses. Obviously this is not due necessarily to poor control but is something intrinsic to diabetes. Thus it should be of little concern since things seem to straighten out over time. I found another study from Florida to be somewhat frustrating. It reviewed the impact of school nurse coverage and medical management plans on diabetic control. They found that both school nurse presence and written diabetes plans resulted in better diabetic control. Children with a school nurse present one to five days per week had better diabetes control (hemoglobin A1c = 7.4%) compared to children with no nurse present (hemoglobin A1c = 8.0%). Children who had a school nurse present five days per week had even better control with a hemoglobin A1c average of 7.38%. Children with a written management plan had better control (hemoglobin A1c = 7.45%) compared to children without a written plan (hemoglobin A1c = 8.0%). *All of our patients have written diabetic plans but the school nurse situation is very frustrating. I fully understand why the school system cannot afford nurses for every school but it may have a very deleterious effect on our patient's control. Maybe in some other life we will be able to supply nurses to the schools and all will be rosy once again.* Finally another study from the Barbara Davis Center in Denver (they were all over the place at these meetings) looked at the apparent epidemic of ketoacidosis in children newly diagnosed with diabetes in Colorado from 2006 to 2009. As they noted "at diagnosis of diabetes, DKA effects disproportionately younger, poorer and uninsured children as well as those from population with low awareness in incidence of diabetes." They compared the presence of DKA at diagnosis from three different time spans and the results are in the following chart:

DKA at diagnosis of diabetes in Colorado children			
	1978–1982	1998–2001	2006–2009
	36%	29%	41%

They felt that the increase in DKA rates in 2006 to 2009 was partly explained by a higher proportion of uninsured patients and those of Hispanic ethnicity among the children diagnosed. They concluded "the apparent increase in the severity of presentation of Type I diabetes in Colorado children over the past twelve years points to a major setback in the community awareness of symptoms and signs of diabetes or in the access to care. The rates of DKA in Colorado children, previously declining, have returned to the 1980s level and are now twice as high as those in Europe". They concluded that the diabetes was being diagnosed less quickly than before. *We do have to take into consideration the number of younger children that are being diagnosed now as opposed to earlier years. These children oftentimes are harder to pick up (particularly the toddlers). It is also conceivable that the onset of diabetes is occurring more rapidly than previously and as a result children become sicker quicker. Nevertheless, we need to be certain that the general population is aware of symptoms of diabetes and comes for help quickly. I do not know the rate of ketoacidosis in our new onset patients over the last few years but I think we could find that out quickly and I would not be surprised if we found that our rates were going up somewhat also.*

A group from Baltimore looked at the use of Lantus either with a pen or with a vial in adult Type II diabetics. I realize that this is not our population but they found that patients using the pen were more inclined to continue giving insulin. They also found a greater hemoglobin A1c improvement 8.0 versus 8.3% in the pen group. Amongst these Type II diabetics pen usage actually was cost effective and saved money over a nine month span. *I know that we have been advocates of the use of pens for insulin, particularly for the rapid analogs when children are at school. We need more studies like this to demonstrate cost effectiveness so that insurance companies and Medicaid will be more inclined to cover them for our patients. Intuitively, control should be better in patients with pens than with vial and syringe but we need studies to demonstrate that in a large number of patients and in children if we are to succeed to make them available to everyone.* A study from Germany looked at the dosing accuracy of common disposable insulin pens. They prefaced the report with the idea that "compared with vial and syringe, insulin pens offer substantial improvements in compliance and flexibility. However, normal glycemic levels in patients with Type I and Type II diabetes can only be maintained if a high dosing accuracy is provided". They compared the SoloSTAR pen with glargine, the FlexPen with Levemir and the KwikPen with Humalog. They used fifteen of each pen and then compared accuracy. "All tested insulin pens revealed an excellent dosing accuracy. The tolerance limits defined by the ISO standards were met by all pens at all tested dosage levels." The following graph shows how remarkably accurate these pens were at doses of 5, 30 and 60 units:

Dosing accuracy



Most of the studies over the last couple of years have shown that pens are in fact probably more accurate than syringe and needle in the average hands. I do not think we have to worry too much about accuracy when our children are using their pens. Another study compared intradermal insulin delivery versus subcutaneous insulin delivery. Intradermal insulin is injected into the outer layers of the skin and is apparently absorbed more rapidly. They had a device that allowed accurate delivery. The following graph shows that intradermal insulin is in fact somewhat faster than subcutaneous insulin:

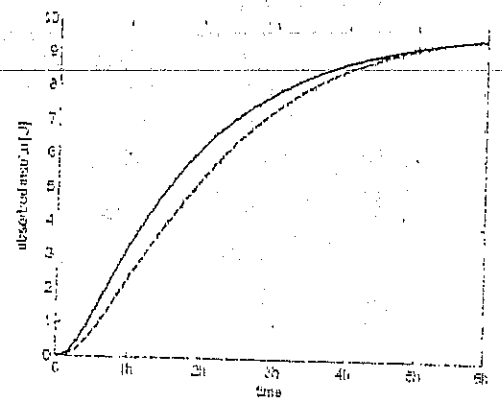


Figure: Cumulative absorption of a 10 U insulin Lispro bolus delivered subcutaneously (dashed line) and intradermally (solid line)

In both cases Humalog was used. *I do not know how clinically significant this difference is but it may be another way to speed up delivery of insulin to overcome some of the problems that I mentioned earlier.*

There were remarkably few presentations on self blood glucose monitoring this year. There were no new meters that people were trying to hype and the emphasis has been very much on continuous glucose monitoring for the last couple of years but I did want to mention a study from Israel that looked at a non-invasive self blood glucose monitoring device that could be used for home use. They pointed out that the main concern in non-invasive (no blood drawing) methods is to achieve high accuracy. They felt that an alternative approach to increase the accuracy is to combine three non-invasive glucose measurement methods to come up with a single result. They have a device called the GlucoTrack that uses ultrasound, electromagnetic and thermal testing. The three results are weighted and have a smaller impact of interferences, leading to more accurate, real time glucose readings. With this device the calibration procedure takes about one and a half to two hours and will last for one month without further calibration. The Clark Error Grid analysis showed that 96% of the points were in zones A and B and 60% were in zone A. This is considered very acceptable accuracy. When the device was used on a day without further calibration, 96% of the points were in the A and B zones and 57% were in the A zone. Thus calibration is valid for long-term. They concluded "the present model of GlucoTrack gives promising results. A key benefit of the device is its long intervals between recalibrations and the ability to perform frequent spot measurements without the need to continuously wear the device." *I did not see this device and have no idea its size. I suspect it is not miniaturized at this point. Nevertheless, there may come someday where we can determine glucose measurements without drawing blood or interstitial fluid. Hopefully that would lead to better compliance from our patients but only time will tell.* There was another device from Switzerland called the Multi-Sensor Glucose Monitoring System which features "non-invasive sensors for dielectric as well as optical characterization of the skin and underlying tissue in a wide frequency range." They found that 89% of the results were in the Clark A and B zones which again showed remarkably good accuracy. *Again I do not know the size of the machine and I have no idea of its practicality. It will be very interesting to see what develops over the next few years.* There were several seminars and multiple abstracts presented on psychosocial issues. I have chosen not to report on them this time. Our clinic social workers are aware of the research and incorporate it into their practice when applicable. The ADAPT group from our clinic did not present a paper this year. However, they are to be congratulated on the number of papers that they have published about our patients. Many of you were participants in the ADAPT study and I want you to know that the psychologists have done a wonderful job with their information and have shared a good deal of new insight that you helped provide.

So there you have it for this year. I have consciously tried to shorten this masterpiece and hope that I have succeeded. Only after it is revised will I know if I was successful or not. I should mention that 13,000 people attended the meeting this year. I do not know how that translates into gallons of sweat when they all walked out of the convention center. I know of no fatal cases of dehydration, however. The meetings next year will be in San Diego and I suspect you will have a much happier reporter. I hope that this information has been helpful to you. If you have any questions of course ask me in clinic.