Rob Lindsay, M.D.

Second City Rehash

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Well, we are doing it once again. I am hoping that this will be a much briefer and more to the point summary than it has been the last few years. The meetings were held in Chicago this year and unfortunately I was sick during much of the session. That did not keep your intrepid reporter from attending, however. Chicago was interesting in that it was in the 90's each day and yet it rained every day. The Cubs were in town but playing day games and I could not afford to miss any sessions so there is no baseball to report on. It was fun to see old friends and be updated but overall the meetings were fairly uninspiring this year.

<u>Diabetes Control and Complication Trial/Epidemiology of Diabetes Interventions and Complications</u>

The first session upon which I would like to report was the DCCT/EDIC results update. You will remember that the DCCT (Diabetes Control and Complications Trial) was the first study to absolutely document that good control had a profound effect on long-term health and complications. Dr. David Nathan reviewed the DCCT briefly. The planning started in 1983 and patients were recruited between 1983 and 1989. It was reported out in 1993. EDIC (Epidemiology of Diabetes Interventions and Complications), which was the follow up study, reached its 30 year anniversary this year and they wanted to update what they had found. The DCCT was designed to explore the glucose hypothesis that good control prevented complications. If you remember, there were two groups: the primary group had had diabetes for one to fifteen years and had no complications while the secondary group had had diabetes anywhere from one to fifteen years and did have complications. The intensive group received three or more shots per day or was on pump therapy. They also tested their blood at least four

times per day. The goal was to have the pre-meal blood sugar between 170 and 120 mg/dL and the post-meal glucose less than 180 mg/dL (*This sounds very similar to what you all are taught now*) and the desired hemoglobin A1c was less than 6.05%. Unfortunately that goal was not met. The conventional patients were generally on two shots per day, tested less and did not have close follow-up. The conventional group had an overall hemoglobin A1c of 9% while the intensive group had an A1c of 7%. One thousand four hundred and twenty-two of the 1,440 participants completed the study. In the primary group (which virtually all of you would be considered to be equivalents) had a 76% reduction in retinopathy and a 52% reduction in nephropathy with intensive therapy. The resulting problems were a threefold increase in severe hypoglycemia and a 4.6 kg weight gain. All of these results have been reported to you in the past in this forum.

EDIC was to follow the microvascular and severe microvascular complications in the same patients after they finished the interventional study. After the completion of the DCCT, the patients were returned to their own physicians and maintained control as best they could. The intensively controlled group in the DCCT had a rise in hemoglobin A1c and the conventional group had a drop in hemoglobin A1c so that during the years of EDIC, they had virtually identical control. These patients were followed up to 30 years and maintained whatever control they and their doctors were able to achieve. They were all offered intensive training after completion of the DCCT and 96% participated. The mean hemoglobin A1c for the first 20 years was 8.0%. At 18 years, 1,278 patients were followed which was 96% of the surviving participants making it a very statistically significant study. Dr. Lloyd Aiello presented the retinopathy (eye disease) update. He introduced the concept of metabolic memory. They looked at the average hemoglobin A1c of each individual over the time span of the DCCT and found that in EDIC, there was a 53% increased risk of retinopathy for every 1% higher the DCCT A1c average had been. Thus years later, the patients who had had good control during the DCCT still showed significantly less risk of retinopathy. If we look at the numbers over the years, the intensive group from the DCCT had a 70% reduction in retinopathy at year 4 of EDIC, a 53% decrease in retinopathy at year 10 and a 46% decrease at year 18. He said that the control during the DCCT accounted for 86% of the difference in the rate of retinopathy when comparing the intensive and conventional patients. If we look at degrees of retinopathy, there was a 47% risk reduction for severe retinopathy, a 35% risk reduction for macular edema and a 39% reduction in risk for laser therapy at 18 years of age. Again at 18 years after the DCCT, the intensively controlled group had a 48% reduction in ocular surgery, a 44% reduction in vitrectomy, a 48% reduction in cataract extraction and a 50% reduction in any type of severe retinal outcome. Thus he concluded that that period of intensive care was critical to long-term good health.

Dr. Ian de Boer reported on nephropathy (kidney disease). In the DCCT there was a 34% risk reduction of any kidney disease overall for the intensive controlled group versus the standard controlled. At 8 years of EDIC, there was a 57% decrease in risk of any type of kidney disease and at 18 years there was a 39% risk reduction of kidney disease for the intensive patients. He was looking specifically at microalbuminuria which is what we test when we obtain urine specimens from you. It is the first sign of significant kidney disease and at 8 years there was an

84% decreased risk in the intensively controlled group and at 18 years a 61% decreased risk. Looking at hypertension, at 20 years study in EDIC there was a 60% incidence of high blood pressure but there was a 20% risk reduction in the intensively controlled versus conventionally treated patients. When looking at end state renal disease (this is the point where patients require kidney transplant or dialysis), there was a 50% risk reduction in the intensively controlled group. Once again there was definite metabolic memory. John Lachin reported on cardiovascular risk reduction. There was no statistically significant difference during the DCCT between the two groups. In EDIC, coronary arterial calcification (thickening of the arteries of the heart) was reduced 50% in the intensively controlled group. If we look at clinical cardiovascular disease, there was a 42% reduction in risk of myocardial infarction, angina and stroke. When they looked for the duration of EDIC, there was a 57% reduction in stroke, myocardial infarction and cardiac death. For every 10% drop in hemoglobin A1c there was a 21% drop in the risk of severe cardiac disease. *These results are rather amazing. Remember that these patients had virtually identical control after the DCCT was completed. Even so, that period of tight control during the study had a profound effect on their long-term health. This merely emphasizes once again how critical it is that we try to keep the hemoglobin A1c as low as possible and that we maintain due diligence even at a young age. Many of these DCCT patients were enrolled as teenagers and so we cannot just blow off the teenage years as a difficult time to control diabetes and "we will do better later". We must maintain control from the very beginning if we are to ensure that all of our children have a safe and healthy life.*

Council on Diabetes on Youth

Next I wanted to review the session of the professional section interest group discussion on diabetes in youth. This occurred over the lunch break on Sunday. Crystal Jackson from the ADA reported on the Safe in School program. She reported that the challenges are exactly what you encounter frequently. She listed them as 1) failure to have trained staff in the schools, 2) refusal to administer insulin to students, 3) no coverage during field trips and extended care after school, 4) refusal to allow tests in the classroom and 5) refusal to allow students to attend the school at all. The Safe in School campaign is designed with three main goals: 1) all school staff members have some knowledge of diabetes, 2) school personnel must be trained to perform basic diabetes tasks and 3) children who are able to do so can self-administer. There are legislative efforts ongoing and a case before the California Supreme Court. The ADA is also launching a new childcare initiative for children under 5. She mentioned that we can obtain the free Safe at School toolkit at shopdiabetes.org.

Dr. Jamie Wood discussed the Type I Diabetes Exchange. She was looking primarily at the ability of pediatricians to meet the ADA goals. Remember that the ADA says the hemoglobin A1c should be less than 8.5% for children less than 6 years of age, less than 8% for children 6 to 12 years of age and less than 7.5% for teenagers 13 through 20. The other goals were a blood pressure less than the 95th percentile and an LDL (the "bad cholesterol") less than 100 mg/dL. She reported on the 13,316 patients in the Type I Diabetes Exchange (I described this study last year). Forty-eight percent are girls and the duration has been four years. Overall

32% of the patients have achieved the hemoglobin A1c goals. Sixty-four percent of the patients 1 to 5 years of age have an average hemoglobin A1c of less than 8.5%. Forty-three percent of the 6 to 13-year-olds have an A1c of less than 8% and 21% of the 13 to 20-year-olds have an average A1c of less than 7.5%. If you are interested, 79% of the younger patients were on pumps whereas it was 50% in the middle age group and 24% in the older age group. There was wide variety between the various participating centers in their degree of success: some had 50% of their patients within range, down to some that had 17%. I unfortunately was not able to copy down all of the blood pressure and lipid results but I included the goals so that you can see where you stand.

Dr. Darrell Wilson from Stanford and Dr. William Tamborlane from Yale participated in a debate as to if these goals were possible or not. They were arbitrarily assigned the topic and made note that they were just serving as devil's advocates to make the discussion interesting. Dr. Wilson felt that the goals were basically unrealistic with the current therapies. He felt that the main goals really should be DKA avoidance, pregnancy avoidance, smoking avoidance and alcohol avoidance. In addition we should have no retinopathy and hypertension and that if there is microalbuminuria, it should be treated with ACE inhibitors. He stated that the ADA goals that I quoted above were not evidence based and were merely expert consensus. Thus we do not know what our goals in glucose control should truly be. He felt the real goal should be that there is progressive improvement in diabetic control. He felt that we needed good evidence based data before truly assigning a goal. Dr. Tamborlane felt that the goals are very much possible. He pointed out that virtually all of his patients at Yale have a hemoglobin A1c of less than 7.5%. He felt that pump therapy was providing a tremendous improvement in overall control. He quoted two studies in which pump therapy was compared with multiple daily injections. The patients on pump therapy had hemoglobin A1c levels of 7.2% and 7.6% while the MDI patients had A1c's of 8.1% and 8.2%. He pointed out that in the JDRF continuous glucose monitoring study the pediatric patients had a decrease in hemoglobin A1c of 0.8% to an average A1c of 7.2% if continuous glucose monitoring was used consistently six times per week. He reported that in his Yale group, 7% had a hemoglobin A1c of less than 6.0%, 29% had an A1c of 6.0-6.9%, 33% had an A1c of 7.0-7.9%, 19% had a hemoglobin A1c of 8.0-8.9% and 12% had a hemoglobin A1c of greater than 9.0%. In the Type I diabetes exchange on the other hand, the children less than 6 years of age had an average A1c of 8.3%, between 6 and 12 years of age an average A1c of 8.3%, between 13 and 17 years of age an average A1c of 8.7% and between 18 and 26 years of age and average A1c of 8.6%. Thus not all centers can produce the same results as Yale. (*This has been an ongoing debate over the years as to how Yale seems to manage to do so much better than other centers. There still is a question about their patient enrollment and retention*). He reported in his group that the risk of retinopathy was less than 2% per year after 10 years duration of diabetes which is a far cry from what it used to be. In his tighter controlled group there is 0% retinopathy. Dr. Wilson pointed out that in the JDRF studies with continuous glucose monitoring there were still less than 50% of the patients that were able to achieve less than 7.5% hemoglobin A1c averages. He also pointed out that in the STAR1 study, less than 50% had a hemoglobin A1c average of less than 7.5% and that even in the best centers across the country (other than Yale) less than one-half of the patients reached goal. Dr. Georgeanna

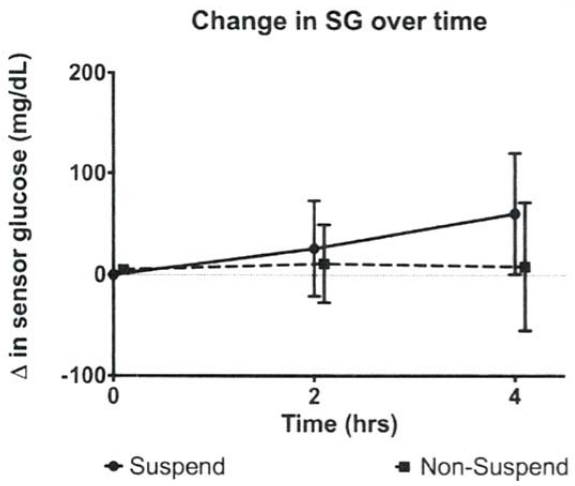
Klingensmith from Denver reported from the audience that when patients have a hemoglobin A1c of greater than 8.5% the barriers are not just a matter of dosing. She felt that any patient with an A1c that high should have depression screening. She also reported that looking at home self-blood glucose monitoring and downloading the results at home could have a significant beneficial effect. *I had several take home messages from this session. First, the ADA goals appear worthwhile and we should strive to achieve them but we really do not know if these truly are the goals that we should have. As Dr. Wilson pointed out, we need evidence based information so that we can fully understand what our patients should achieve. The group from Yale is a very selected group and is very different from most centers across the country. The Type I diabetes exchange was described in the handout last year and I think that that is a much more indicative group of where our patients really are. Our numbers are very similar to those. As a matter of fact, the results that I record each year from clinic are actually somewhat better than the national results. Nevertheless, none of us are achieving the kind of control that we very likely need to achieve. Although all the experts agreed that better control is absolutely necessary for the pediatric diabetes population, none of them had particularly good advice as to how to improve it. We still have the dilemma that most of our patients are not adequately controlled and thus are not safe.*

Closed Loop Pumps

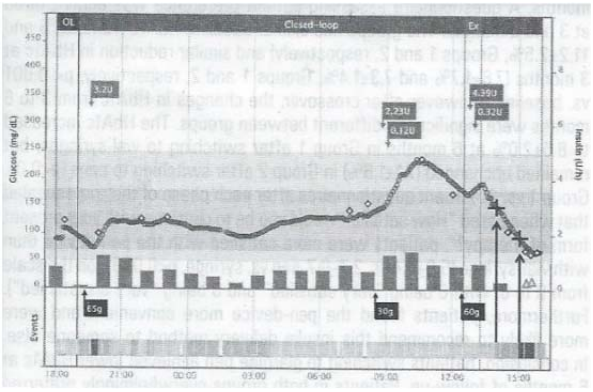
On Saturday I went to a session sponsored by Diabetes Care on a variety of topics. The one I want to report on, however, is the first which was by Boris Kovatchev on "Feasibility of Out-Patient Fully Integrated Closed Loop Control-First Studies of Wearable Artificial Pancreas". He reported a study from Virginia using a cell phone platform. They used a Dexcom Seven continuous monitor and an Omnipod pump. They used a smartphone with Sony Bluetooth as the connector. It also was able to show the continuous glucose monitor tracing. The system was used for 830 hours but 549 of the hours were closed which meant that the system ran itself without patient input. They were able to maintain inter-device communication 97% of the time when the system was closed and 99% of the time when it was open. The target range for blood sugars was 70 to 180 mg/dL and they were able to keep within that target range 68% of the time. Overnight it rose to 72%. The number of hypoglycemic episodes that resulted from a glucose level of less than 70 mg/dL was 0.27 events per 24 hours. They had used this system with a

computer inpatient and so they compared the inpatient and outpatient results. Seventy-four percent of the inpatient time was spent between 70 and 180 mg/dL while it was 70% outpatient (this included both open and closed). During the night, 74% of the time inpatient was between 70 and 180 mg/dL whereas 72% of the time at night while on the outpatient system was spent within range. The frequency of hypoglycemia was very similar. There were 0.24 episodes per 24 hours inpatient and 0.27 events per 24 hours outpatient. They felt that the real time remote monitoring worked well. *This is one of the first studies to look at a cell phone platform to communicate between a continuous monitor and a pump. Obviously there is still quite a ways to go but this is a major step forward. Those of you who are hoping eventually for an artificial pancreas should take great heart with this type of study.*

There were several abstracts presented on closed loop pumps. The first was a study from Beijing, China that was encouraging to me. I admit I did not understand all that they did but basically they were using a new system that was based on standard clinical parameters. What they were trying to devise was something that the average physician can use. They found that it was very "effective in achieving normal glycemia and has excellent robustness to unannounced meals. The simplicity of the proposed method makes it physician friendly, so it has great potential for extensive use". They prefaced their study by saying that "the existing artificial pancreas control algorithms are generally too complicated for a physician to understand". *I agree with them entirely and am comforted to know that there are some studies going on to allow for Closed Loop Pump for Dummies. I certainly will fit in that dummy category*. The group from Northridge, California presented a poster on "Pre-Clinical Safety and Efficacy Study of an Overnight Closed Loop System". They used seven diabetic dogs and found that they could achieve very good overall performance in a closed loop system using Medtronic devices. "The average percentage time in range (70-180 mg/dL) was 95.4%, mean blood glucose ranged from 99 to 153 mg/dL, and the blood glucose concentration never fell below 80 mg/dL". *Again these studies are showing better and better accuracy and efficacy. This will come about and you will all be able to benefit from it eventually.* Another problem with the continuous monitor, of course, is that if the blood sugars should drop low, the system cannot infuse sugar to bring the blood sugar back up. The approach many people are taking is a suspension of insulin delivery when it appears that the patient is going to become hypoglycemic before it happens. This allows the patient to keep the blood sugar out of the hypoglycemic range and in fact gradually raise the blood sugar level. A group from Yale presented a study showing the effect of the two hour suspension of basal insulin on elevating nighttime sensor glucose concentrations. They were using a Medtronic Veo system that automatically interrupts basal insulin for two hours if a patient fails to respond to low glucose alarms. Seventeen Type I diabetics were in the study and wore a blinded sensor (this means that they cannot see the sensor levels) on 71 nights when the basal insulin infusion was pre-programmed to include a two hour zero basal rate at random times after going to sleep. They found that the serum glucose rose by 26 mg/dL by the end of the two hour suspension and by 61% two hours later. They concluded that "automatic suspension of basal insulin for two hours is an effective and safe means of limiting the duration of nocturnal hypoglycemia in patients with Type I diabetes".



Boris Kovatchev presented a poster on the efficacy of outpatient closed loop control. They used 21 patients for two 38 hour outpatient sessions. They used the Diabetes Assistant based on the Android smartphone. During the sessions, the patient operates DiAs via graphical user interface. The DiAs receives continuous glucose monitor data from the Dexcom Gen 4 sensor, runs the CLC (closed loop control) algorithm and controls the Tandem T Slim insulin pump. The DiAs "manipulates basal rate to maintain normal glycemia overnight, administers corrections during the day, suggests free meal insulin upon entry of estimated meal carbohydrates and predicts/mitigates hypoglycemia". The graph shows how they succeeded and they concluded that the first studies of the outpatient CLC show control performance similar to previous inpatient studies. *This is another study from the same group that I mentioned earlier.*



A group from Jacksonville looked at patient response to overnight closed loop control. They were actually working with a group from Cambridge, United Kingdom also. They were not reporting blood glucose control but rather the patient's acceptance of this system. Their results are in the following chart.

Table: Usability of the closed-loop component categorised into Good or Excellent, Fair and Poor (None of the adolescents rated any aspect as Terrible). Data shown are percentages.

	Good or Excellent (%)	Fair (%)	Poor (%)
1.Accuracy and reliability of performance	71.4	28.6	0.0
2.Ease of start-up, calibration, etc.	62.5	12.5	25.0
3.Instructions, manual and technical support	62.5	12.5	25.0
4.Screen information and reports	50.0	37.5	12.5
5.Alarm functions	42.9	57.1	0.0
6.Size, weight, appearance and fashion issues	37.5	37.5	25.0
7.Battery life and ease of replacement	37.5	12.5	50.0
8.Variety and flexibility of functions	37.5	50.0	12.5

As you can see, these systems are not universally welcomed at this point. They will need a good deal of fine tuning before they can be considered acceptable for the general patient. However, they certainly are becoming more popular and are getting closer to true availability. There were several other posters presented with the use of artificial pancreas at home for a short period of time. For the most part all of the results were encouraging. I am not going to go into each individual study but just wanted you to know that they are being evaluated extensively across the world. *Although we still have a long way to go, we are making exceptional strides forward. I would never have predicted that we would be this close two or three years ago. These systems will not be available in the immediate future but are very much on the horizon. I have no idea what the cost will be and I have no idea how much training the patient, parents and care providers will need to undergo in order to make them safe. Nevertheless progress is marching forward.*

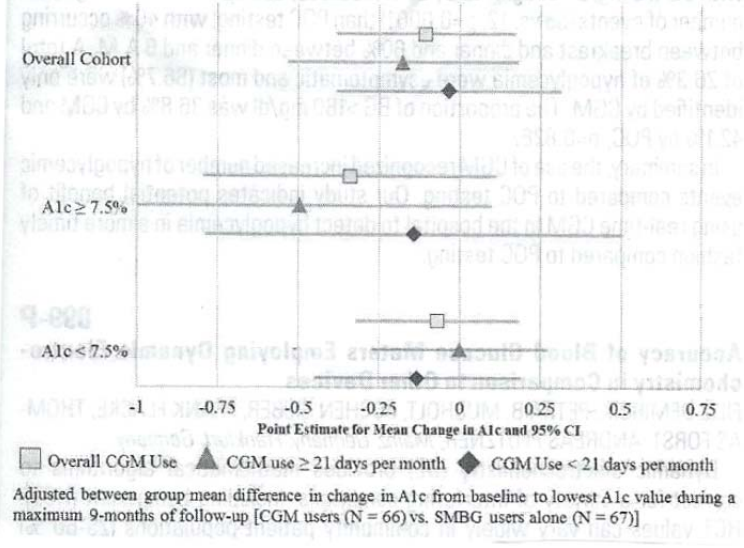
<u>Continuous Glucose Monitoring</u>

Continuous glucose monitoring continues to be the bright star new kid on the block. I did not go to any official sessions on the devices but there were many posters and abstracts that were presented plus there was a commercial symposium that I attended. First I wanted to report on a study from Salt Lake City. This is by Dr. Jim Chamberlain who used to be at the Diabetes Center on the adult side and he is now at St. Marks. He looked at the differences between the two continuous monitors and how it may influence the frequency of usage. Specifically he was looking at the DexCom SEVEN and the Medtronic MiniLink REAL-Time monitors. He found that 19% of the Medtronic users wore their device almost daily whereas 76% of the DexCom users claimed to do so. Sixty-five percent of the Medtronic users wore their device less than one week per month compared to only 3% of the DexCom users. When questioned why the difference in use, he found "31% of MiniLink users reported 'CGM did not seem accurate' as the main reason for less frequent use". There also was difference in pain and irritation. He concluded "differences in perceptions of performance and usability may strongly influence frequency of continuous glucose monitoring use, which can impact clinical outcomes". *If you*

remember from previous years, it has been shown that the continuous monitor is useful in terms of lowering the hemoglobin A1c only if it used at least six days per week. When used less than that, it has no impact on A1c levels. This study shows a definite difference between the two companies. I was struck at several sessions where people from the audience mentioned that their patients simply would not use the Medtronic monitor and that the reported poor usage rates were more with the Medtronic than they were with DexCom. Medtronic is coming out with a new monitor that they promise will be more accurate and less painful. Then we may have an equal playing field but at the moment DexCom seems to be the preferred choice.

A study from the Barbara Davis Center looked at effectiveness of CGM in adult patients with Type I diabetes. They did not report which brand of monitor the patients were using but they did report that there was some improvement with the continuous glucose monitoring when the A1c was compared to previous A1c levels. Specifically, the patients who had an A1c of greater than 7.5% showed a significantly greater drop than did the patients whose A1c was already less than 7.5%. In the patients with the higher initial A1c, you can see that the frequency of use again played an important factor. They felt that the reasons for low adherence included cost, high frequency of alarms and discomfort. I do not know how well the patient was able to determine the accuracy of the monitor.

Figure 1. Difference in Mean Change in A1c by Baseline A1c



Adjusted between group mean difference in change in A1c from baseline to lowest A1c value during a maximum 9-months of follow-up [CGM users (N = 66) vs. SMBG users alone (N = 67)]

A group from San Diego and Idaho Falls looked at the performance of the DexCom Generation 4 in 30 patients between 2 and 17 years of age. They found that there were no serious adverse events or infections. There was mild skin irritation in 3% of the sites but no other adverse events were reported. The monitor readings were within 20% of the concurrent blood glucose test 77% of the time. The clinically accurate A zone was 76% and the A plus B zone was 98% (*Remember we have defined these Clark zones in previous summaries*). Skip readings were less of a problem. The system performed consistently between 6 A.M. to 6 P.M. 76% of the time and

at night 79% of the time. The system provided glucose readings on average 92% of the time with 81% of the sensors lasting to day 7. They concluded "the clinical accuracy, on time and sensor life of the systems all compared favorably to the CGM system currently approved for pediatric use." *You need to remember that the DexCom has only been approved for use in patients 18 years and older. They were comparing their results to the Medtronic monitor.* The Barbara Davis group also reported on differences in patients who continued to use CGM versus those who discontinued its use. Here again they did not differentiate between brands. They found that "the most common reasons patients self-discontinued CGM were accuracy, numerous alarms, skin reactions/sensor discomfort and cost". They found that there was minimal difference in the reduction of hemoglobin A1c over a six month span between those who continued the monitor (0.63%) versus those who discontinued (0.32%). These were all adult patients. *Thus again they found that the continuous monitors did not have a tremendous beneficial effect*. The group from Charlottesville, Virginia looked at early clinical and psychological impacts of first time glucose monitoring users. I will not go through all their numbers but they found that the adults in this study demonstrated an increase in trait anxiety and depression. In addition behaviors aimed at reducing hyperglycemia decreased while those aimed at avoiding hypoglycemia increased by the end of the study. They concluded that "some patients may initially exhibit worsening psychosocial characteristics, including those related to hypo/hyperglycemia-related anxiety and trait anxiety and depression". They felt that more research on the psychological effects of the monitors would need to be preformed. *There were many more abstracts presented at the meetings but these give a feel for what people are finding. My impression after attending these sessions was that the DexCom Gen 4 is probably the best player on the market at the moment. It seems to be accurate enough and has less discomfort. The concerns about anxiety and depression would apply to it equally as to any of the other monitors that are available clinically or experimentally. For the first time I feel that one of the monitors is accurate enough that I would feel comfortable with its use. I do not feel comfortable with the Medtronic monitor at the moment but they are coming out with a new one and then all bets will be off. Presumably it will be more comfortable and more accurate since the company is acutely aware of the problems. I still believe that continuous glucose monitoring will be the wave of the future. This will be particularly the case when we have consistent communication between the monitor and the pump. It will have a place for our patients on shots also. At this point our clinic is not recommending that people switch over but we are willing to talk to patients on a case by case basis.*

Blood Glucose Monitoring

Although continuous glucose monitoring may be the darling of the future, blood glucose monitoring remains the staple at this time. There were no sessions devoted to meters, however, since it is old hat. There were quite a few abstracts and posters dealing with the topic. First I would like to report on a study from Renton, Washington. They looked at the comparative accuracy of six different blood glucose monitoring systems. They looked at the Contour Next, the ACCU-CHEK Aviva Nano, the FreeStyle Lite, the One Touch Ultra, the One Touch Verio and the True-Track. They compared the meters with a Yellow Springs Institute machine (this is what is used for all basic comparisons) and used the mean absolute relative difference (MARD) as the main comparison. They looked at the MARD both in the hypoglycemic range and the overall range. What they found was "when compared with other blood glucose monitoring systems, Contour Next demonstrated the lowest mean deviation from the reference value in the low and overall glucose range". Remember that the lower the MARD, the closer the meter is to the control system.

Table 1. MARD Comparisons to the CONTOUR® NEXT BGMS

		Low glucose range (YSI <70 mg/dL)			Overall glucose range (YSI 21–496 mg/dL)		
Sample type	Meter system	N	MARD (mg/dL)	*P* value*	N	MARD (mg/dL)	*P* value*
All samples	CONTOUR® NEXT	135	4.28	NA	538	3.09	NA
	Accu-Chek® Aviva Nano	135	7.24	<0.0001	538	4.17	0.0468
	OneTouch® Verio™ Pro	134	9.47	<0.0001	536	5.23	<0.0001
	OneTouch® Ultra® 2	135	20.91	<0.0001	537	10.84	<0.0001
	Freestyle Lite®	135	6.08	0.0048	538	9.60	<0.0001
	Truetrack®	135	24.24	<0.0001	538	12.32	<0.0001
Unmodified samples	CONTOUR® NEXT	85	3.51	NA	438	3.07	NA
	Accu-Chek® Aviva Nano	85	5.99	0.0001	438	4.02	0.0003
	OneTouch® Verio™ Pro	84	7.83	<0.0001	436	4.80	<0.0001
	OneTouch® Ultra® 2	85	15.96	<0.0001	437	9.61	<0.0001
	Freestyle Lite®	85	4.05	0.9385	438	9.31	<0.0001
	Truetrack®	85	13.56	<0.0001	438	9.70	<0.0001

MARD, mean absolute relative difference; YSI, Yellow Springs Instruments; NA, not applicable; HSD, Honestly Significant Difference.
*Versus CONTOUR® NEXT as determined using Tukey's HSD methodology. *P* values <0.05 are considered significant.

A group from Germany evaluated six meters and found that five of them were in compliance for both of the criteria. The ACCU-CHEK Aviva was within range 95.6% of the time for low blood sugars and 99.1% for high blood sugars, the BG*Star was 99.3%/97.5%, the iBG*STAR was 98.5% and 97.5%, the FreeStyle Freedom Lite was 95.6% and 96.5% and the One Touch Ultra 2 was 95.6% and 96.3%. Only the Contour failed the low blood glucose range (90.4%) but was accurate 97.5% overall. Thus this study contradicts the one I just presented. Another study from Tarrytown, New York looked at five different blood glucose monitors and I have included their chart for comparison with the other studies.

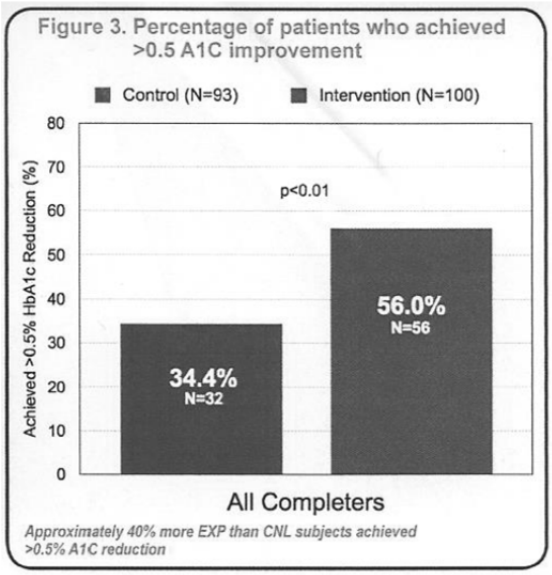
Table 1. MARD Comparisons to the CONTOUR PLUS BGMS

	Overall glucose range n=314 YSI 27-460 mg/dL	Low glucose range n=93 YSI ≤ 80 mg/dL	High glucose range n=113 YSI > 180 mg/dL
Meter system	MARD mg/dL	MARD mg/dL	MARD mg/dL
CONTOUR®PLUS	3.35	3.43	3.26
Accu-Chek® Performa	4.95*	4.55	6.0*
Accu-Chek® Active	5.84*	6.42*	5.58*
OneTouch® SelectSimple	10.32*	12.87*	9.43*
FreeStyle Freedom™	14.69*	17.11*	13.49*
* CONTOUR®PLUS MARD statistically significantly lower in this range.	YSI-YSI glucose analyzer, YSI Inc. Yellow Springs, OH		

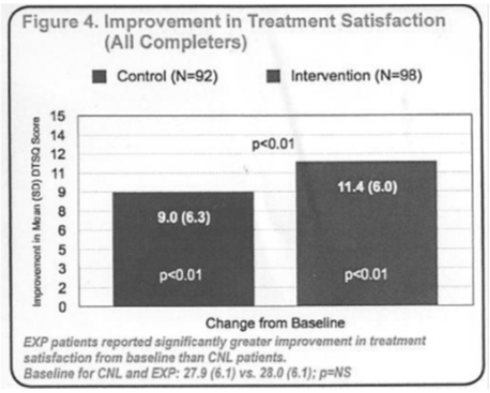
They concluded that the Contour Plus had a significantly lower MARD than the others. Thus each study has slightly different results. The study from Germany showed the Contour to be less accurate but I do not believe that was the Contour Plus. That may be the difference between the studies. As you can see, most of the meters meet published criteria but there is a difference one meter versus another.

Another study from Pennsylvania looked at the One Touch Verio meter. This is the meter that reports patterns rather than just individual numbers. They compared how much time it took the care provider (physician or nurse educator) to find patterns using a logbook versus the time it took using the meter with its patterning on the screen. The care providers took about four minutes to go through a logbook where it took about a minute to determine the same patterns via the meter. About 70% of the healthcare providers felt using the meter was easier than reviewing a logbook. They concluded "in summary, using the new One Touch Verio meter was four times faster and more accurate than using logbooks to help healthcare providers identify blood glucose patterns". *We had some significant problems with the One Touch Verio and, as many of you know, it was taken off the market briefly. It is now back on and I am more than happy to have patients utilize it. Notice that none of the earlier studies compared the accuracy of the One Touch Verio. The important thing will be if patients can learn to utilize the patterning that the Verio demonstrates. Physicians and educators are good at looking at patterns and that is basically what we do when you come to clinic. We want everyone to be able to do patterning at home frequently so that changes can be done more acutely. The Verio may enable us to have patients do more patterning and thus have better control although we do not have good studies of long-term use yet.* Another study from Germany looked at three different meters at temperatures of 12 degrees, 25 degrees and 38 degrees. I will not compare the meters nor go over their absolute numbers. They found that cold temperatures led to more frequent device errors. *We need to remember this problem during the winter particularly with our skiers. We need to try to keep the meters and their strips relatively warm so that we have as much accuracy as possible. Obviously this is particularly important on the slopes.* There were four studies from a variety of places looking at the ACCU-CHEK Expert meter. I have not seen this meter but it

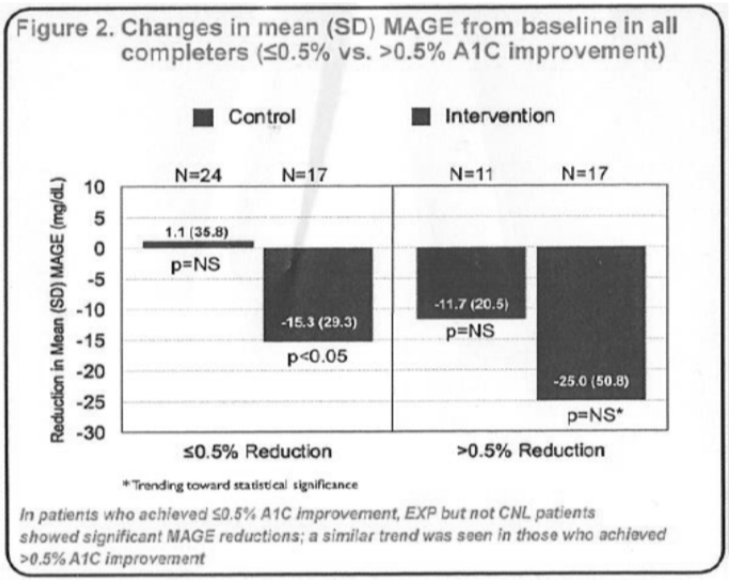
has an automated bolus advisor. They compared two groups of patients, the control group used a standard blood glucose meter and calculated the bolus insulin doses manually whereas the experimental group used the ACCU-CHEK Expert meter with its automated bolus advisor which told them exactly how much insulin to give. One study looked at the percentage of patients who achieved a goal of a greater than 0.5% hemoglobin A1c improvement. I have included their chart which shows that there was a significantly better response in the patients who used the advisor.



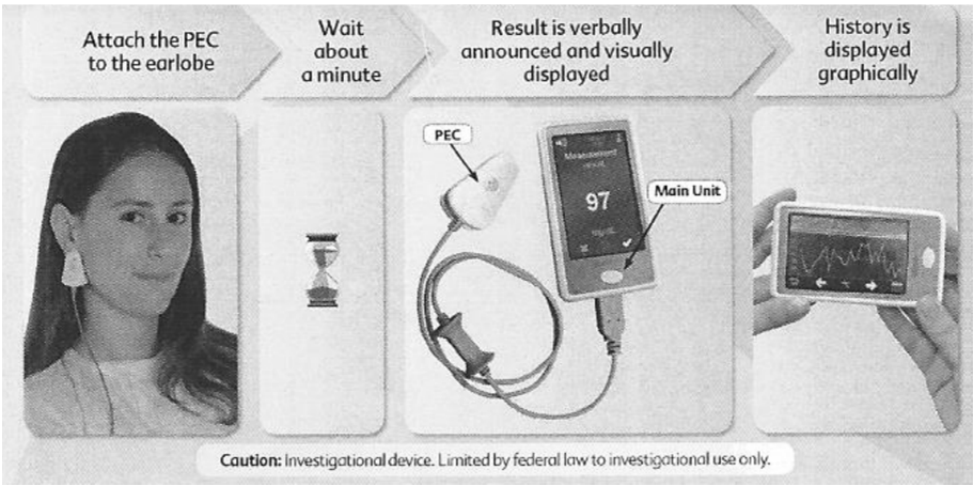
Patient satisfaction with the advisor was also statistically significant.



Another study looked at the advisor in patients who intermittently wore continuous glucose monitoring. They were looking specifically at the MAGE which is a marker for glycemic variability. Again you can see that with the advisor the MAGE dropped significantly more than it did in control patients. The difference was considerably greater in the patients who had a hemoglobin A1c improvement of greater than 0.5%.



They concluded that the use of the automated bolus on the meter significantly improved control and reduced glycemic variability. *First off we have no access to this meter so I cannot really address it firsthand. Secondly, because the ACCU-CHEK use in the intermountain area is so low, we do not even have a drug rep at the moment. Third, this looks interesting and if it applied to the standard pediatric patient might be worthwhile as long as the cost was not too great. We talked quite a bit about glycemic variability last year and as you know that is a critical factor in preventing long-term complications. If this meter would help us reduce the variability (hence the hyperglycemia) it might be very useful. Hopefully we will be able to see this meter in the not-too-distant future*. Finally there was a study from Israel presenting a truly non-invasive glucose monitor. This is a system called the GlucoTrac device which is basically an attachment on the earlobe. There has to be about a one minute wait before there are results and they were investigating its accuracy. I have included a set of pictures that they provided to show the size.



They found that the device was within the Clark Error Grid A and B zones 96.2% of the time. They looked at its use over six months and I have included the chart that shows their data.

No degradation in performance was noticed as a function of time elapsed from calibration (Table 1).

Table 1: Device Accuracy as a Function of Time Elapsed From Calibration

Time from calibration	# of Data Points	CEG A+B zones (%)	CEG A zone (%)	Mean ARD (%)	Median ARD (%)
1 month	6,204	96.3	41.7	30.7	24.5
2 months	436	98.4	40.4	29.6	23.7
3 months	371	96.0	37.2	31.9	28.4
4 months	472	96.0	43.0	29.7	24.0
5 months	390	94.6	43.8	28.5	23.2
6 months	366	95.1	38.3	31.0	27.3
Accumulated	**8,239**	**96.2**	**41.5**	**30.5**	**24.7**

Seventy-two percent of the patients using the device felt it did not cause any discomfort while an additional twenty-five percent tended to agree with that assessment. Interestingly, only 56% of the patients fully agreed with the statement that "when the device will be approved, I will monitor my blood glucose levels more often". Again 56% said that when the device will be approved "I will use it regularly". They concluded that it demonstrates acceptable accuracy and had high satisfaction. *I would have expected an even greater degree of satisfaction given that it was non-invasive. Eighty-two percent tended to agree or fully agreed that they might use it more often and 87% fully agreed or tended to agree that they would use it regularly. This is not available yet and I have no idea when it will become marketable. There is a time issue that a lot of our patients might not like. It will be interesting to see what transpires.*

So there you have it on meters for the moment. Nothing dramatic but general progress and I must admit that we have much better accuracy than we had years ago. Self blood glucose monitoring is still the standard in diabetes care and it's reassuring to find out that the accuracy continues to improve and we can rely on it even more comfortably.

<u>Insulin Pumps</u>

The last session of the meetings on Tuesday was a symposium on the current state of insulin pump therapy. We were all thoroughly exhausted and most people had already left so I can report only so much. I unfortunately had to miss the last section on "Low Glucose Suspend" by Dr. Timothy Bailey in order to get to the airport. I felt badly because this is a topic that will be coming up soon. The first speaker was Phillip Raskin who is a grand old man of diabetes. He was talking about the use of pumps in Type II diabetes, a topic of little interest to the patients in our clinic. Certainly as we find more Type II patients, pump therapy will become a question but at this point it really does not pertain. I did think that he had some good points that would apply to Type I patients, however. He felt that the criteria for patients to go on pumps included 1) sub-optimal control, 2) motivation to pursue intensive control, 3) the frequent use of self-blood glucose monitoring, 4) sufficient education, 5) adequate psychological stability, 6) appropriate

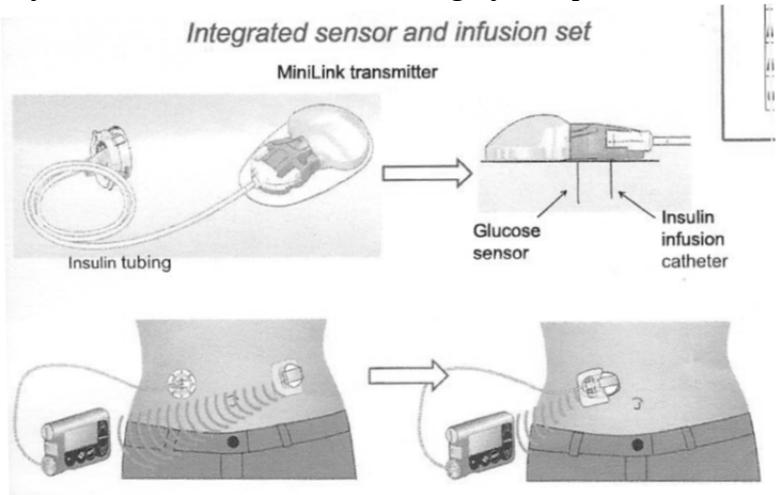
financial status and 7) a well trained staff. *I think these criteria apply equally to our Type I patients.* He felt that the main benefits were flexibility, the fact that it was more physiologic in nature, that the delivery was more predictable and that in general patients had less hypoglycemia. He again pointed out that for pumps to achieve truly good control, a patient should be doing five to seven blood glucose tests per day. It is only when they are testing frequently that pumps improve overall A1c levels. (*Did you hear this, oh my patients?*)

Dr. Howard Zisser talked about insulin patch pumps. He pointed out that the Omnipod is the only patch pump truly available right now. It became available in all states in 2008 and most of the artificial pancreas studies have been using the Omnipod pump. You are all fairly familiar with the Omnipods so I will not review it right now. He did point out that in day three it is very common that most patients require more insulin. *I think this is an interesting point and something we ought to evaluate. We may need to have a different basal rate for the third day for our patients.* He also talked about some of the other pumps that may become available. Roche has the Medingo patch pump that has a bolus button. This is the pump I mentioned two years ago when I was at the Roche/ACCU-CHEK booth. It enables a patient to give extra insulin if the MDI is not immediately available. This pump is being used in Europe but is not available in the U.S. Cellnovo has a patch pump that allows wireless data transmission. The Jewel pump from Debiotech is a very small patch pump that is made cheaply. He felt that it was very precise in its delivery. The handheld device for control also contains a meter. This pump is not available in the States but may well be so in the near future. He also listed a few other simpler patch pumps that are considerably less adjustable than the ones I mentioned. He felt they were "wearable pens". The PaQ has a bolus button and each push will yield 2 units. The VGo has a pre-set basal rate and again a 2 unit bolus. It will allow for several basal rates. Finally the Finesse has pre-set basal rates and will give 1 or 2 units per click. He reported that a study showed 90% of patients preferred pod pumps to pumps with tubing. The study also showed a decrease in hemoglobin A1c from 7.1% to 6.8% in those patients tested. He said the main reason was because the patients never disconnected their pod pump. It has been shown that the blood glucose value increases 1 mg/dL for every minute a tube pump is disconnected. That blood sugar oftentimes remains elevated for hours. Hence the slightly better hemoglobin A1c in patients on pod pumps. *I understand all that he said but I very much doubt that 90% of our pump patients would choose pod pumps over tubing pumps. We had quite a bit of difficulty with the earlier Omnipod falling off. This problem seems to be resolving and the newer smaller Omnipod seems well tolerated. It only came out this summer, however, so we need more time to know its characteristics and patient acceptance.*

Finally Dr. Rubina Heptulla talked about combination infusions. She pointed out that all of these pumps are at the stage of proof of concept. That means that none of them are in further stages of evaluation and none will be available in the near future. She stated that these pumps were being developed because of three main difficulties with pump use. Number one was the immediate post-prandial (after meals) hyperglycemia that I have been harping about for years. Number two was the pre-prandial hypoglycemia that frequently occurs and Number 3, overall poor control despite pump use. One of the problems is that there is glucagon dysfunction in most

of our patients also. The glucagon has a paradoxical effect and increases after meals. It also tends not to increase in response to hypoglycemia. Thus researchers are looking at a dual insulin/amelin pump since amelin suppresses glucagon after meals. Thus pramlintide administration would lead to glucose suppression and decreased post-meal hyperglycemia. In early studies better control was achieved with the combination of insulin and amelin. However they still do not have a normal glucose profile. Exenatide is a GLP1 receptor agonist which suppresses glucagon post-prandially and also delays gastric emptying. They found that there was much less glucose excursion when both insulin and pramlintide were infused at the same time. However the main side effect is mild nausea which causes many patients to not use it. Finally he talked about a closed loop glucagon and insulin pump. It helps prevent the hypoglycemia prior to meals but does not help the post-prandial hyperglycemia that we encounter. *These are all very interesting and will be considerably more expensive and more complicated to use. In the long run, however, we may find that one of these options is very useful. At the moment, I still think that proper timing of insulin before meals (where have you heard this before?) is the most critical factor. Once we have more rapid acting insulins the post-prandial excursion will be considerably less important.*

There was only one abstract on pumps that I wanted to mention this time. MiniMed submitted an abstract on the feasibility of the MiniMed Duo device. This is a device that combines both the glucose sensor and the insulin pump infusion set. They are both inserted together and there is only one combined device in the skin. I have a picture of the device along with the earlier separate pump and continuous monitor. As you can see there are two inserts, one for the sensor and one for the catheter. They both are small steel needles that presumably would be less likely to kink. There is communication between the sensor and the pump. However it is not a closed system in that the patient has to tell the pump what to do with the insulin. The concern was that there might be greater glucose error when the sensor needle is so closely placed to the infusion catheter. The data showed very good accuracy. Ninety-six point three eight percent of the readings were in the A-B Clark Error Grid. The results were virtually identical to when the two devices were separate. The patients felt that this was a relatively painless device and the large majority of them found the Duo to be highly acceptable.



They presented initial information with the Duo last year at the meetings. *This study merely confirms that it is a viable option. If their patient survey is accurate, the complaint of pain with the sensor apparently is considerably less than I reported with the earlier devices. I suspect MiniMed will be putting this device before the FDA as soon as it can. I will be very interested to see how it is accepted. The one drawback is that it is still a pump with tubing. Ultimately it would be nice to have a pod connected to the sensor so that we would not have the tubing and external pump involved. Nevertheless, this is a definite step forward.*

Insulin and Insulin Delivery

Monday afternoon I went to a symposium that was quite involved entitled "Update on New Insulin Preparations for the Management of Diabetes". The first speaker was Mary Korytkowski on the clinical use of concentrate insulin formulations. In this case she was talking about U500 insulin. This has no use in pediatrics but there are apparently patients with Type II diabetes and extreme insulin resistance that can take upwards of 600 units of insulin per day. As you can imagine this would be a very large volume either by shot or by pump. Thus they are working on a U500 insulin that would give you 500 units per cc of fluid. You all use U100 insulin so this would be five times more concentrated. She talked about the studies using this insulin. She said on the horizon there may be U300 Lantus. These will never come into your hands. Then Dr. William Cefalu talked about "Alternative Insulin Delivery Systems-Inhaled, Oral, Patches and Microneedles". He first talked about micro-needles which are micron sized needles that go into the viable epidermis and therefore do not cause pain. It can be put on with a patch or the insulin could be coated on the needle. These are very much in the experimental stage and he thought that they might be useful for nighttime control. He mentioned that the first studies on nasal insulin were 18 years ago and he stated that there really was nothing new on this front. Buccal insulin is insulin that is sprayed into the inner cheek or to the back of the mouth. The main concern with this is that it may take up to 10 sprays per meal. He said that this system is being reviewed by the FDA but for this to be at all viable (primarily for Type II diabetics) they would have to figure out how to need less puffs per dose. The problem with oral insulin is that it has to get to the gut through the acid of the stomach and then be absorbed by the mucosal wall. He questioned the effect of this on the liver. He said that there were various ways to overcome

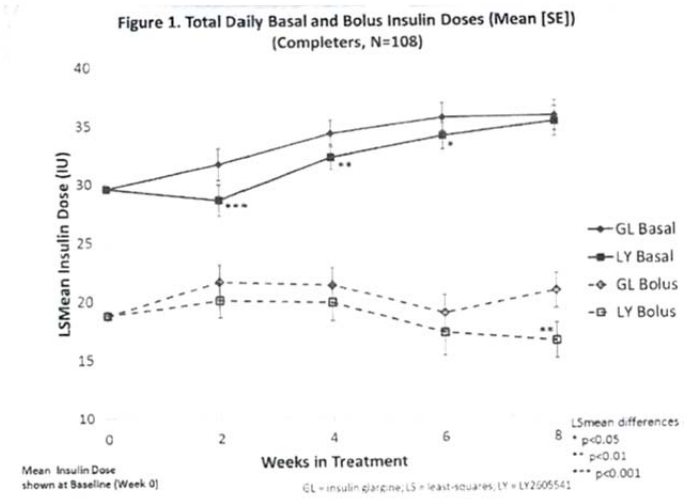
the basic problem including IN-105 which is an insulin polymer. The two hour post-prandial (after meal) blood sugars are proportionate to insulin given subcutaneously. He thinks that this is being developed by Squibb. He also mentioned ORMD from Israel which does reduce mean glucose levels. There are some trials ongoing in the United States. Capsulin is an enteric coated insulin that is absorbed primarily in the jejunum and duodenum. It can achieve insulin effect and there are some phase two studies going on. He stated that Novo is working on an oral insulin but had no information and they would not share information with him. Finally there are some hepatic directed vesicles that target the hepatocytes in the liver. However these are not a priority at this time and there is little research going on. He pointed out that inhaled insulin has been a major disappointment and most companies have pulled out of its development. It has very rapid uptake that is determined by particle size. The concern is the effect on underlying lung disease. Mannkind is still working on the Technosphere. It does reach the lung, has more rapid uptake than subcutaneous insulin and there is a linear dose absorption relationship. The research continues but this is the only inhaled insulin that is being evaluated now that Pfizer has taken their insulin off the market.

Then Dr. Thomas Donner talked about new subcutaneous insulin formulations. He said the main question would always have to be if the newer developments are better than current formulations. The main goals would be that they attain normal glycemia, minimize severe hypoglycemia and minimize weight gain. He pointed out that the current analogs cause less hypoglycemia in children than the old regular insulin did. He feels that they do a good job but they still have a delayed onset of action and they last too long. Thus we end up with post-prandial (remember this is post meal) hyperglycemia and pre-prandial hypoglycemia before the next meal. He again emphasized that we should be giving the insulin 15 minutes before eating. *Please remember this since you are getting tired of me telling you and I am getting tired of telling you.* He then went into basal insulin. Degludec is the insulin that was produced by Novo and has been approved in Europe. It forms soluble multihexamers that have a half life of approximately 25 hours and a duration of 42 hours. Thus the insulin can be given anywhere from 8 to 40 hours between shots. In Type II diabetics they have identical control to that of Lantus. The degludec has a flatter profile than does Lantus so it produces 16% less hypoglycemia and 36% less severe nocturnal hypoglycemia. There does not seem to be a major change in hypoglycemia during the day. It requires a slightly lower dose than Lantus. In studies thus far there have been no changes in A1c levels when patients switched from Lantus to degludec. The problem here is that the advisory committee to the FDA voted eight to four to release degludec on the market and Novo had hired salesmen in preparation for releasing it this spring but then the full FDA chose not to approve it and insisted on further cardiovascular studies. This will put its release back two to three years. *This was a major blow. Degludec was supposed to be the major introduction at these meetings and of course it could not be. I was very much looking forward to its use and thought that it would replace Lantus very quickly. Oh well.* He also talked about the insulin LY2605541. This is an insulin made by Lilly and works primarily by being a polyethylene glycol moiety and it increases the liver uptake. When compared with Lantus, there is a slight weight loss with its use. Most studies show identical hemoglobin A1c results although there was one study that showed slight improvement. There

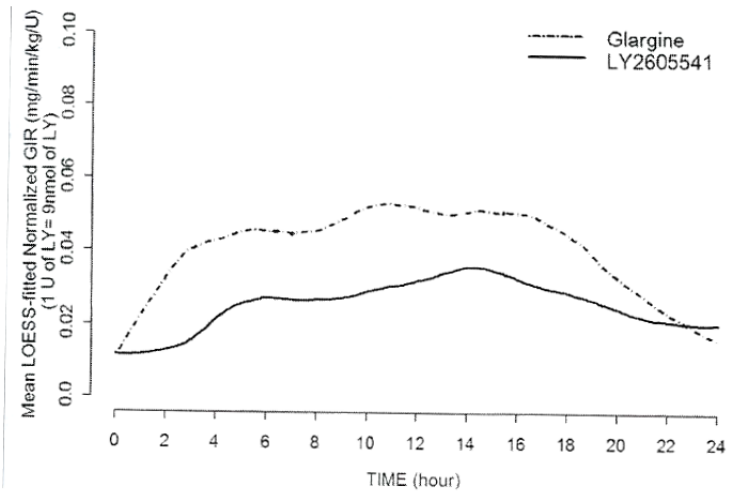
was a slight increase in liver enzymes although the ALT was still normal. It led to 10% lower glucose levels during the daytime and a 17% reduction in meal time dose. It has less variability than Lantus so that it is somewhat smoother. There are five ongoing Phase three trials. *I suspect that this will now be the first alternative to Lantus to be available. Obviously Lilly was delighted when Novo had to go back to the drawing board with the degludec. I think that this insulin may well be out in another year and a half or so but it is all dependent on the vagaries of the FDA.* He then went into bolus insulin. He said what we need is (obviously) faster more immediate acting insulin. This would give better post-prandial blood sugars and if there is more rapid clearance there would be less pre-meal hypoglycemia. With more rapid clearance there also could be less weight gain. He said ideally the insulin should be so fast that it could be given even after eating. He talked about hyaluronidase which I had mentioned quite a bit last year. It causes more rapid absorption and more accelerated pharmacokinetics. He stated that there really was no injection site pain. It led to more rapid absorption, a higher peak level and more rapid clearance. The hyaluronidase is continuing to be studied and I will mention an abstract about it in a little while. He also mentioned FIAsp. This is an insulin made by Novo that combines nicotinamide plus arginine plus NovoLog. It has been studied in pigs and shows lower post-prandial blood sugar levels and a much more rapid peak. There have been no human studies thus far. (*I will resist pig/patient comments.*) He is optimistic about new forms. He mentioned a nasal insulin that could lead to decreased nighttime hypoglycemia and less weight gain. He also mentioned smart insulins. These insulins would work only when glucose levels were elevated. I have absolutely no idea how they would work and he said there is no data on them thus far. There is apparently research ongoing, however. Finally Dr. Celeste Durnwald talked about insulin strategies in pregnancy. I will not report on her presentation since it has little bearing to our clinic. It did give some very good insight with insulin and newer insulins. *I felt the session was very interesting and useful. None of this is available yet but it is encouraging that people are continuing to work on these different aspects. As we have learned over the years, we will need many different approaches for one to work. Thus if there are enough studies ongoing, surely something will come up in the not-too-distant future.*

There were several abstracts on some of the newer insulins. A study from Miami looked at the variability of degludec versus glargine (Lantus). They looked at 9-point profiles (nine blood sugar tests done throughout the day) in patients and compared day to day variability in each of the patients with themselves. Unfortunately there is a good deal of variability even when the patients are doing the same activity and eating the same things. They found that within subject variability was 7-10% lower with degludec than it was with Lantus. *This means that we have a better chance of having more reproducible blood sugars day to day with degludec than we do with glargine.* Another study out of Denmark (Novo) looked at degludec and how it works. They concluded that degludec multihexamers are composed of micrometer long linear arrays of hundreds of insulin hexamers. "The ultra long duration of action for insulin degludec relies on the formation of soluble multiple hexamers in subcutaneous tissue, and the protein fold adopted by insulin degludec in these multihexamers is very similar to that of human insulin".

A study from Dallas that was sponsored by Lilly looked at improved glycemic control despite reductions in bolus insulin doses with basal insulin LY2605541. They did the study because there had been earlier observations that patients on LY2605541 required less prandial insulin than when patients were using Lantus. They studied 108 patients for eight weeks and looked at the insulin bolus requirement of these patients. When the patients were on LY2605541 they required statistically significant less Humalog at breakfast, lunch and dinner and there was an average reduction in daily bolus dose of 4.3 units per day. They also found that there was less nocturnal hypoglycemia but slightly more overall hypoglycemia with LY2605541. They concluded "LY2605541 treatment compared with GL (Lantus) in patients with Type I diabetes demonstrated lower daily mean glucose, less nocturnal hypoglycemia but more total hypoglycemia, resulting in a need for lower meal time insulin doses, which may reflect a more prolonged duration of basal insulin action or greater suppression of hepatic glucose production". The differences are illustrated in their chart with the upper levels being the amount of basal insulin required and the lower level being the amount of bolus insulin required.



Then of greater interest was a study also supported by Lilly that showed that LY2605541 insulin has a flatter glucodynamic profile than Lantus at steady state. I will not go into their study but I will show the graph which shows a significantly flatter profile and thus a "potentially more stable and predictable metabolic control".

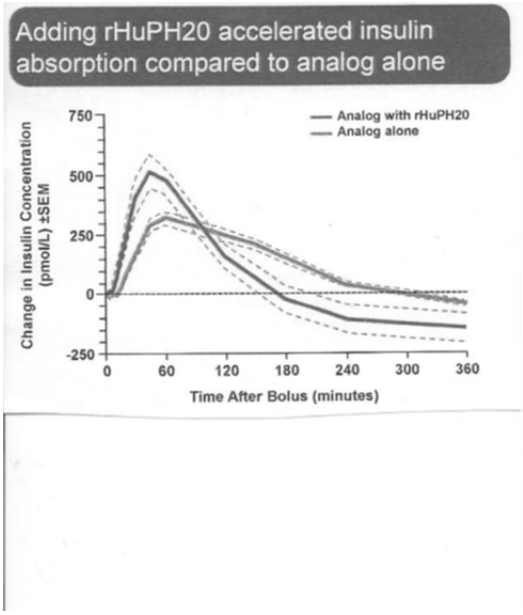


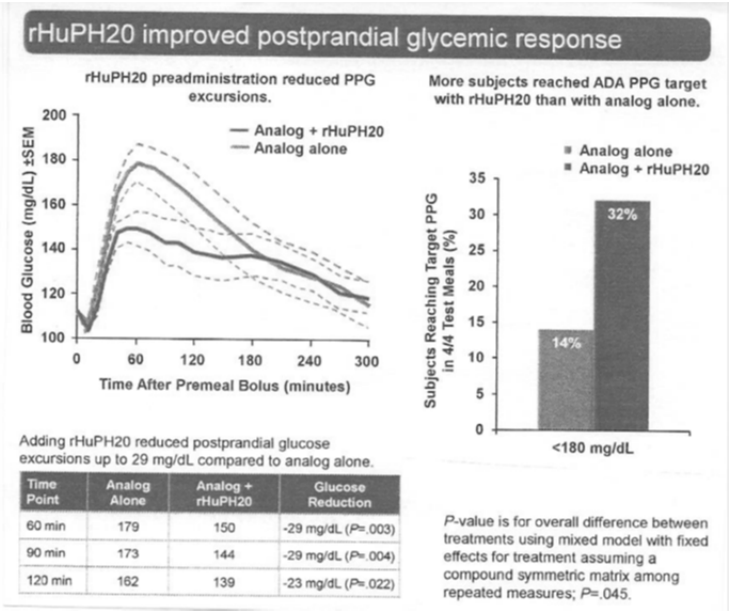
Lantus has always been considered the most stable of our long-acting insulins and indeed it has a much flatter curve than did our earlier NPH or Ultralente. However, it was soon discovered that Lantus is not entirely as smooth as we would like and that there is definitely an early hump and a later hump with its use. This graph, if reproducible in other studies, indicates that we could rely on a more steady effect of LY2605541 insulin than we do with Lantus. This would be a significant improvement in overall control. I hope that this proves to be the case in our hands when we start using the insulin.

There were also a few abstracts on insulin delivery. A group from Germany further reported on the InsuPad. I reported on the InsuPad last year which is the device that enhances insulin absorption by standardized warming of the insulin injection site. This study was looking at real world conditions and used 78 patients, some of whom were Type I and some Type II. During the study patients using the InsuPad had an improvement of hemoglobin A1c from 6.8% to 6.2%. The control group was virtually similar going from 6.8% to 6.3%. However the difference was in the amount of insulin needed. The standard group had to increase their daily prandial insulin by 12%. The group using the InsuPad, on the other hand, had a 20% drop in prandial insulin doses (bolus insulin) and a slight increase in the total basal insulin. Overall the total daily dose increased in the control group by 5.2% and decreased with the InsuPad by 8.3%. They concluded "use of InsuPad for three months resulted in a lower frequency of hypoglycemic events and a reduction in insulin requirements as compared to the control group under real world conditions. InsuPad may be useful to achieve a safer and more efficient basal bolus therapy in insulin treated patients with diabetes". *Remember that the InsuPad is used with a pump infusion set and is not useful for patients on injections. Nevertheless it sounds very interesting. They did not comment on how well tolerated the device was.* Finally I have another report from Israel on the InsuPad. I am almost afraid to bring this up because I do not want this idea to be misinterpreted. They reported that "the device applies local controlled heat to the skin in the vicinity of the injection site which promotes local blood profusion and enables faster absorption of the insulin from the injection site". This study was done in Type II diabetics and they found that the post meal injection of insulin was better than when the insulin was given without the

InsuPad prior to a meal. They concluded "the use of the InsuPad device enabled 30 minutes post-meal injection with better post-meal glucose control. This added flexibility when using the InsuPad device may have benefit in subjects with unpredictable eating patterns". *Please remember that these are Type II diabetics which is very different than our patients with Type I diabetes. I do not want people to immediately assume that they can start bolusing after they eat. On the other hand, this device might be very useful for our toddlers on pumps who have to take insulin after they eat because they are so erratic in how much they will take. I will be curious to see if they find the same type of results in Type I diabetics but I am dubious.*

Another study from San Diego looked at the use of hyaluronidase with insulin pumps. Remember hyaluronidase breaks down hyaluron which forms a barrier to bulk fluid flow of subcutaneously administered drugs. The hyaluronidase, by breaking down these barriers, allows more rapid spread of drugs and thus presumably a faster absorption. They used 1 mL of hyaluronidase by bolus as the infusion set was placed every three days. They reported that the hyaluronidase was well tolerated and that it reduced post-prandial glucose excursions up to 29 mg/dL when compared to infusion without the drug. Early hypoglycemic risk (soon after eating) was similar but late hypoglycemic risk was reduced. Their results can be seen on the chart and the two graphs that I have included.





Adding rHuPH20 reduced postprandial glucose excursions up to 29 mg/dL compared to analog alone.

Time Point	Analog Alone	Analog + rHuPH20	Glucose Reduction
60 min	179	150	-29 mg/dL (*P*=.003)
90 min	173	144	-29 mg/dL (*P*=.004)
120 min	162	139	-23 mg/dL (*P*=.022)

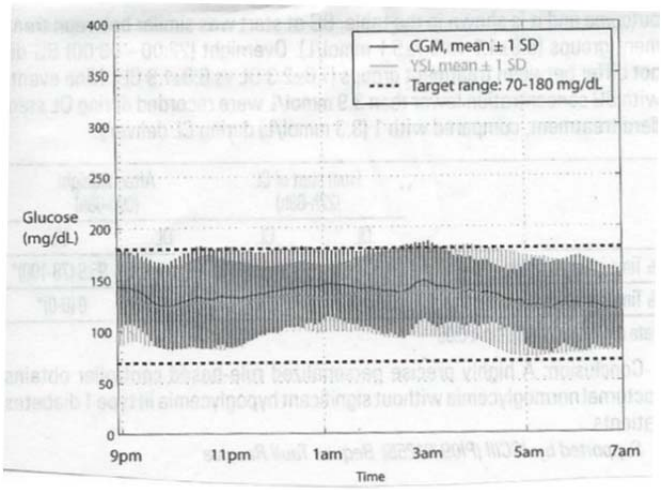
P-value is for overall difference between treatments using mixed model with fixed effects for treatment assuming a compound symmetric matrix among repeated measures; *P*=.045.

If hyaluronidase is truly as well tolerated as they claim, this would greatly aid the absorption of insulin and make timing less of a concern for those on pumps. The first graph shows the change in insulin concentration and as you can see with hyaluronidase the absorption is faster, higher and disappears quicker. The glucose changes are predictable. With hyaluronidase the post-meal glucose is not as high and there is less drop but at least in this study the pre-meal glucose for the next meal was very similar. I still think that this is an interesting approach that may bear fruit for our pump users. Unfortunately it cannot be translated to injections at this time. The group

from Barbara Davis Center in Denver looked at the use of a pen versus vial or syringe with Lantus. They did a crossover study where they did vials for three months and then used the Solostar pen for another three months. One group started with the pen and the other group started with the vial. They found that the group that started with the pen had a definite increase in hemoglobin A1c after switching to vial syringes but the group switching to the pens stayed stable. The patients were more satisfied with the pen device than the vial syringe and "overwhelmingly preferred glargine pens over vial syringes". *The difference in control is a matter of the patients getting their insulin. If a patient prefers the pen, he is more likely to take his insulin routinely. I have always felt that Lantus pens were less important than the Humalog or NovoLog pens because the shots are given at home and there is less of a convenience factor. Apparently there may be an advantage to using the Lantus pens also.*

<u>The Journey to a Viable Artificial Pancreas</u>

I realize that I have already talked about closed loop pumps but this was a session on the first day of abstracts that were presented on various aspects of working toward an artificial pancreas. I just thought you would be interested in what they had to say. The first was a study from Palo Alto and Colorado in which they added hyperglycemia mitigation to predictive low glucose suspension. They were using a Kalman filter based pump suspension algorithm (*whatever that is*) to prevent nocturnal hypoglycemia. They reported that the algorithm provided a 50% reduction in the continuous glucose monitoring readings that were below 70 mg/dL with an increase of 11 mg/dL in mean morning glucose levels. In this study they added a hyperglycemia mitigation to create a "control to range" type of algorithm for the full day. They based this algorithm on the 1800 rule for insulin sensitivity. They assumed that the current basal rate is constant through the day and amounted to 50% of the total daily dose. The algorithm determined the excessive glucose and divided by the insulin sensitivity to get a correction dose. Before using both the hypoglycemia and hyperglycemia mitigation in an open loop setting, there was an average of 0.98 interventions per day. When both algorithms were in place with a closed loop system there was an average of 0.43 interventions. They concluded that adding hyperglycemic mitigation lowers risk and the number of glucose related alarms at night and during the day. They felt good overnight control is feasible. The next study was from Pennsylvania and was set in a clinical research setting. They used the hypoglycemia-hyperglycemia minimizer system which is somewhat akin to what I reported above. During the hospitalization, the HHM system, comprised of an insulin pump, continuous glucose monitor and controlling algorithm dosed automatically based on the CGM values. The mean overnight value was 135 mg/dL by CGM and 129 mg/dL by lab instrumentation. In 20 patients studied over night, 1.7% of the readings were greater than 180 mg/dL, 93.8% were in the 70 to 180 mg/dL range and the rest were less than 70 mg/dL. They concluded "these results demonstrate that the HHM system was capable of maintaining safe glucose levels overnight, and indicate feasibility for continuing development".



Another study from Santa Barbara looked at inpatient evaluation of an automated closed loop controlled range system. The controller was challenged by over and missed bolus meals and a period of exercise. It was designed to demonstrate that the closed loop system met a set of predefined metrics for efficacy and safety. The attempt was to keep the blood glucose between 70 and 180 mg/dL. They used an Omnipod pump. During the first session, the subjects ate a meal that was not announced to the controller. During the second session they also added an hour of moderate exercise in the afternoon and a second breakfast was over bolused by 30%. For the adolescents in the study, the median percentage of time in target was 61% during the day and 88% during the night. When compared to their outpatient results, this was a significant improvement since during the day they were within range 44% of the time and during the night 41% of the time. Obviously they felt that these results were encouraging and should lead to further study.

Another study from Spain used a rule based algorithm personalized to each patient through his/her prescribed therapy based on the patients past data. They were then tested in both an open loop and closed loop system overnight. The results are in the following chart.

	From start of CL (22h-08h)		After midnight (00h-08h)	
	OL	CL	OL	CL
% Time in target range	60 (17-69)	93.3 (70-99)*	66.6 (18-75)	95.8 (78-100)*
% Time for which BG < 3.9 mmol/L	3.3 (0-16)	0 (0-0)*	4.2 (0-21)	0 (0-0)*

Data are median (IQR). * $p < 0.05$

For clarification, 3.9 mmol/L is the equivalent of 70 ng/dL is how we measure glucose in the States. They concluded “a highly precise personalized rule based controller obtains nocturnal normal glycemia without significant hypoglycemia in Type I diabetes patients”. A study from Israel utilized a MD-Logic artificial pancreas. This consists of a sensor, pump and a fuzzy logic controller with learning algorithm that creates real time individual patients tuning and safety

algorithm to prevent hypoglycemic events and reduce technical issues. (*Not surprisingly I was lost very quickly as they tried to explain this.*) They then did four night studies in the patient's home. These results were compared to four overnights with sensor augmented pump therapy. They have not got enough data yet to fully analyze their results. They stated however "the time that patients spent with glucose levels less than 60 mg/dL and greater than 180 mg/dL was significantly shorter and patients spent more time within range of 70 to 140 mg/dL". This information will be much more analyzed and there will be larger numbers by next year. A group from Portland utilized a bi-hormonal system using both insulin and glucagon. They call their system the Adaptive Proportional Derivative Algorithm. This component includes recurring estimates of insulin sensitivity utilized to modify insulin delivery gain factors. The overall blood glucose average was 135 mg/dL (139 md/dL during the day and 127 mg/dL at night). The mean glucose increment from the start of the meal to two hours post meal was only 30 mg/dL. The automated delivery of glucagon successfully prevented blood glucose values falling below 60 mg/dL in 91% of the cases and below 50 mg/dL in 100% of the patients. They concluded "fully automated insulin and glucagon delivery using the APD algorithm effectively controlled BG levels without a need for precise CHO counting in adults with Type I diabetes. This degree of glycemic control would be expected to avoid long-term complications". *Ultimately this is what we are looking for. To be truly an artificial pancreas, we must have a system that does not require the patient to input insulin for carbs. This approach relieves the need for accurate carb counting and remembering to bolus. For our fairly airheaded adolescents, this would be a godsend. Obviously these systems are still a ways off but ultimately this is what we are hoping for*. Finally there was a study from Santa Barbara and Montpellier, France looking at an intraperitoneal insulin delivery device called the DiaPort made by Roche. The port is surgically implanted and then regular insulin is infused via their system into the intraperitoneal area. They then can use an automated system much like described above. They found that the peak post-prandial glucose was on average 56 mg/dL lower than when the patients were using subcutaneous insulin. With the intraperitoneal delivery, the glucose was kept 47% of the time in the 70 to 180 mg/dL region during post-prandial periods as compared to 23% of the time in the subcutaneous tests. They conclude that "the initial results from the study demonstrated the benefit of faster and reliable insulin administration for glucose control, especially for the AP period". *Please keep in mind that these were unannounced meals so that the pump was responding to blood sugar rises after meals. There was no bolus prior to the meal. All of these studies are very interesting and very preliminary. We will be getting to an artificial pancreas in time but not in the immediate future. Nevertheless, do not give up hope because they are making major strides forward each year.*

Pediatrics

I would next like to go into a few abstracts that were presented that pertained to our age group. The first is from Australia looking at enterovirus infection, vitamin D and islet cell autoimmunity in at-risk children. This was part of the Vigr study which was looking at 313 genetically at-risk children from birth. They were looking for any association between persistent islet cell autoimmunity (remember that virtually all of our young children with Type I diabetes have evidence of autoimmunity which attacks the beta cells) and either viral infection or vitamin D levels. For viruses they specifically looked at enterovirus, varicella zoster virus, cytomegalovirus, herpes simplex virus type 1 and 2 and Epstein-Barr virus. The viruses were detected by PCR in the plasma, throat swabs and stool swabs. What they found was that enterovirus infection was more common at the seroconversion visit (i.e.: the time when the patient became positive for anti-islet cell or anti-insulin antibodies) in children who developed persistent autoimmunity (36% versus 15%). This gave an odds ratio of 3.21 which means the children who had an enterovirus infection had a 3.2 times greater chance of developing persistent autoimmunity. The varicella virus infection at any time (not just at seroconversion) was more common in those with persistent auto-antibodies (25% versus 6%). Interestingly, vitamin D deficiency was not present in any of the patients who seroconverted. On the other hand, children with persistent islet autoimmunity had higher vitamin D levels both at the time of conversion (93.7 nmol/L versus 75.1 nmol/L) and any time before seroconversion. Exposure to cow's milk protein before three months of age was associated with islet cell autoimmunity also. This had an odds ratio of 4.7. They felt the vitamin D deficiency does not have any effect on autoimmunity and that the higher vitamin D levels may reflect early introduction of cow's milk protein based formula. *Enterovirus has been thought to be a possible trigger in susceptible children for years. This is just another study that indicates that that may in fact be true. The cow's milk protein has been an ongoing debate and I really do not know what to say at this point.* A study from New Haven looked at developmental stage at diagnosis and the duration of diabetes in terms of implication for young adolescents with Type I diabetes. They stated that it is recognized that the duration of Type I diabetes impacts hemoglobin A1c, psychosocial adjustment and family functioning. They pointed out that few studies have evaluated patients at the early adolescent stage. Their purpose was "to explore differences in hemoglobin A1c, psychosocial adjustment and family functioning in young adolescents (11 to 14 years of age) by duration of diabetes and

developmental stage at diagnosis". The developmental stage at diagnosis was categorized to infant/toddler/preschool (1 to 5 years of age), school age (5 to 10 year) and early adolescence (after 10 years of age). Their study showed that youth diagnosed for less than two years had a lower hemoglobin A1c as well as higher self-management diabetes care activities and self-management diabetes communication. They could find no significant differences in developmental stage except for hemoglobin A1c where youth diagnosed in early adolescence had a lower level. Psychosocial adjustment and family functioning did not differ by developmental stage at diagnosis although self management was higher among adolescents diagnosed for a shorter time. They concluded "this suggests that young adolescents with longer diabetes duration need additional self-management support during the transition to adolescence to optimize metabolic control". *We have become aware of this over the years. Many of our patients who were young when diagnosed simply did not get the education that our older newly diagnosed patients get. That is why the clinic is providing assessments yearly to try to upgrade basic education for the patient and the parent*. The New Haven group also presented another study looking at clinical outcomes in youth within the second year of Type I diabetes. They found that hemoglobin A1c levels rose substantially between 6 and 12 months after Type I diabetes onset. This correlated well with the insulin adjusted A1c values of less than 9% which indicates that the patient is making less insulin and requiring more via injection or pump. There was a less great rise in hemoglobin A1c from 12 to 24 months despite a further reduction in insulin production. The proportion of participants who switched from injection to pump therapy increased steadily and A1c levels were lower in patients using pumps than those using injections during the first two years. All of these results are in the following chart.

	~2 Weeks	**~6 Months**	~12 Months	~18 Months	~24 Months
	N=561	N=490	N=547	N=566	N=508
A1c *mean ± SD(%)*	11.5 ± 2.3	7.3 ± 1.3	7.8 ± 1.4	8.0 ± 1.5	8.1 ± 1.5
Injections	NA	7.3 ± 1.3	8.0 ± 1.5	8.2 ± 1.6	8.4 ± 1.7
Pump		7.3 ± 1.3	7.4 ± 1.1	7.6 ± 1.1	7.7 ± 1.0
IDAA1c ≤ 9.0%		50%	26%	16%	10%
Pump Use	<1%	14%	33%	39%	44%

They concluded "the metabolic consequences of waning of the honeymoon period may have been blunted, in part, by a concomitant increase in the use of insulin pump therapy". A group from London, Ontario looked at predictors of glycemic control in children and adolescents. There were 996 patients involved between the ages of 2 and 20 years. The Canadian Diabetes Association age specific A1c targets are less than 8.5% for children less than 6 years of age, less than 8% for children 6 to 12 years of age and less than 7% for children greater than 12 years of age. I found that the proportions of subjects with targeted A1c levels at the last visit were 63% for children under 6 years of age, 44% for children 6 to 12 years of age and 9.8% for children greater than 12 years. The distance from a treatment center predicted the target hemoglobin A1c

for those younger than 6 years of age while male gender, longer duration of diabetes and higher BMI predicted target A1c levels among adolescents. A group from Oxford, United Kingdom looked at cyclical variation in hemoglobin A1c values during the year. They found that there were regular oscillations occurring every 6.9 months so that on average hemoglobin A1c values were 0.3% lower during the summer quarter compared to the winter quarter. They also found that the median hemoglobin A1c for the year 2012 was 7.9% with 41% of the children attaining a hemoglobin A1c of less than 7.5%. Children had a lower mean hemoglobin A1c value (7.7%) than adolescents (8.4%). Insulin pump therapy was associated with a lower median hemoglobin A1c value level (7.7%) than multiple daily injections (8.5%). They concluded "these data demonstrate regular cyclicity in hemoglobin A1c values during the year". *We have seen this pattern for many years. I will have to go back to look at my data set to determine the true difference. The summertime enables our patients to be more active and be outside and away from food more frequently. On the other hand, many of our adolescents are less active in the summer since they do not walk to school or take P.E. My impression is that we have seen just the reverse in our St. George clinic where it is so hot in the summer that they do not get the exercise. I will get back to you when I find time to really analyze the data.* A group from Chicago looked at family conflict related to care in adolescents with poorly controlled diabetes. They noted that earlier research showed high levels of family conflict and low levels of parental responsibility surrounding Type I diabetes management have previously been associated with poor glycemic control. In their study they found 1) extremely poorly controlled teens do not report more conflict than those in better control; 2) in poorly controlled youth with Type I diabetes, parents and youth perceive conflict similarly; and 3) poorly controlled adolescents with Type I diabetes report more parental involvement than those with good control. However, they did find that parental and adolescent perceptions of who is responsible for disease related management do not match. Another group from Huntsville, Texas looked at self care among older adolescents with good and poor glycemic control. They found "teens with good glycemic control describe life with Type I diabetes as a struggle, but that they were stronger than the disease. In contrast, teens with poor glycemic control felt that diabetes interfered with their life and that diabetes self care was a burden for which they had to adjust their lifestyle". They concluded "adolescents with Type I diabetes struggle with the complex treatment regimen but those with good control demonstrated acceptance of the disease as part of who they were as a person. Thus diabetes self care was part of their routine". The Barbara Davis group reported "overall, Type I diabetics and non-diabetic adolescents have similarly poor dietary patterns despite Type I adolescents receiving dietary education and support through their diabetes care". They concluded that late adolescence could be an age to target diet interventions. *Go figure*. A study from Sidney, Australia looked at children and teens with diabetes and celiac disease. They found that non-adherence to the gluten free diet led to an early elevation in albumin excretion rate (a marker of early diabetic kidney disease) and were roughly twice as prevalent in the non-compliant celiac patients versus the patients who adhered to their gluten free diet. They could find no association between gluten free diet adherence and neuropathy or retinopathy (eye disease). *Just another reason that our patients with celiac disease really need to stick to the fairly onerous diet. I realize that celiac disease is considered harder than diabetes by many of them but this study merely emphasizes how important adherence is. Hopefully we will find other*

means to control celiac disease in the future. Although there were many more abstracts and posters on children and adolescents with diabetes at the meetings, these were the ones that I thought would be of most interest to you. Before closing this section, however, I would again recommend the book *Ready-Girls*. It is written by Denise Charron-Prochownic from the University of Pittsburgh and Julie Downs from Carnegie Mellon University. It is an excellent pamphlet on reproductive health for girls with diabetes. We should be handing this booklet out to all of our teenage girls and their mothers. I will look to see if we cannot routinely do so. I would highly recommend its use by all mothers and daughters.

Celiac Disease

I did attend a session the first day on gluten related disorders. It was pointed out that celiac disease is present in one million eight hundred thousand people in the United States. Compare this number to thirty-eight million with diabetes. Dr. Alessio Fasano presented a talk on "Celiac Disease-a Clinical Chameleon". He pointed out that celiac disease is present in 1 per 133 people in the United States. The autoantigen is tissue transglutaminase and the environmental trigger is gluten. Elimination of the trigger leads to complete resolution of the disease. Classic celiac disease was seen years ago and was generally picked up in children 6 to 24 months of age. They presented with chronic diarrhea, abdominal distention, anorexia, failure to thrive or weight loss and abdominal pain with vomiting, constipation and irritability. Now we tend to see more a systemic disease that is not usually seen until at least 5 years of age. It presents with dermatitis herpetiformis (a very specific rash), osteoporosis, short stature, delayed puberty, iron deficiency anemia, hepatitis, arthritis and/or seizures. The third component beyond the genetic susceptibility and the gluten is that these patients develop a leaky small intestine. The small intestine is about 20 feet long and is covered by a single layer of cells. The tight junction between the cells can serve as a door. The zonulin gene is located on chromosome 16 which also has some impact on Type I diabetes and rheumatoid arthritis. Gluten is actually a mixture of gliadin and glutenin. These patients cannot digest gluten fully and the remaining fragments lead to the release of zonulin which opens up the tight junctions between the cells. Thus we have the leaking mentioned. There is a drug called Larazotide which is a zonulin inhibitor. Rats treated with this drug will not develop diabetes. It aborts the autoimmune process. Researchers can achieve the same effect if the rats are given a gluten free diet. During

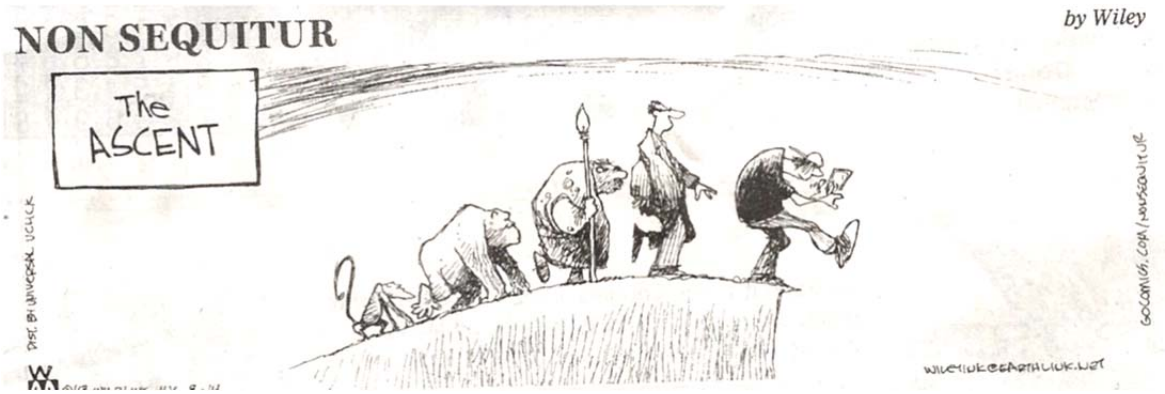
the past 35 years the prevalence of celiac disease has doubled every 15 years. It can even develop in patients in their 70s so there must be some other component that triggers it. They question if it might be due to changes in the microbiotic environment. They also wonder if they can figure out this fourth factor, they might be able to prevent celiac disease and Type I diabetes. *I realize that this is a somewhat garbled summary but it does go to show that there is still quite a bit of research going on in celiac disease.* Carol Brunzel who is both a dietician and a CDE talked about "Meal Planning for Diabetes in Gluten Disorders-Double Trouble?" She pointed out that meal planning for celiac disease is 1) more expensive, 2) requires extensive and repeated counseling, 3) requires an inter-disciplinary team and 4) requires assimilation of a great deal of information. She reported that gluten is primarily in wheat, rye and barley but that there is a good deal of cross contamination with oats and brewer's yeast. There is also contamination in many medications. She recommended a website www.glutenfreedrugs.com as a good reference. She suggested that patients really concentrate on what they can eat rather than what they cannot. She reported that many gluten free grains lack fortification and therefore she encourages more whole grains be used. Many of them are high in sugar and low in fiber and therefore weight gain is a very real concern for our patients with celiac disease. She also brought up cost about which all of you are well aware. She pointed out that packaged meat and poultry are not always gluten free and that it would be important that families call the manufacturers to determine if they are truly gluten free. She also expressed concern about cross contamination. Stores have grains in bulk and there can be contamination there. In homes there can be cross contamination in toasters, mixing bowls and preparatory surfaces. With restaurants there can be cross contamination with serving utensils, pans and grills. Thus our families must maintain very good vigilance if they are hoping to keep their child healthy. Finally Dr. Jessica Markowitz talked about coping with challenges of dual diagnosis. She pointed out that 46% of patients dealing with celiac disease and diabetes complained about the increased cost. Fifty percent found food to be less enjoyable. They complained that the diet was too restrictive and that they were uncomfortable in social settings. Many felt friends and family were afraid to invite them over because they really did not know how to deal with the celiac disease. She reported that depression is found in somewhere between 6 and 57% of patients with celiac disease (*this is a pretty broad range*). The quality of life is lower in women with celiac disease than in men. This does seem to improve somewhat if they are following their diet. The quality of life testing is lower in patients diagnosed in childhood than if they were diagnosed as adults. When you add diabetes to the celiac disease, depression occurs approximately 37% of the time versus another study that showed 17% in celiac disease alone. In her research, there was no real difference in quality of life between patients with diabetes and patients with diabetes and celiac disease. However parents felt that the quality of life was significantly lower for their celiac children. *I find some of this research very difficult since different studies report very different results. My impression is that celiac adds a tremendous burden to our patients with diabetes. Some of our patients do a wonderful job managing celiac and diabetes but many really struggle with it. I wish there were a simpler answer.*

Non-Prescription Therapies for Diabetes Mellitus

This symposium was given on Monday and I found it quite interesting although it was definitely rapid fire. Phillip Gregory, a PharmD gave an overview of agents. He zipped through many but I tried to keep as detailed notes as possible. First he addressed alpha-lipoic acid. It is an endogenous coenzyme that has some antioxidant effect and modulates inflammation. It is used for peripheral neuropathy and can decrease the symptoms score by about 50% in the patients who try it. He did mention that the studies only had gone for at most 35 weeks. There is some effect on fasting blood glucose levels but apparently no real change in hemoglobin A1c. He felt the risks were minimal so physicians should tolerate its use. Second he talked about chromium (usually given anywhere from 200 to 1,000 mg per day). He said that patients with diabetes may be more likely to be deficient (although I believe he was talking about Type II diabetes). In Type II diabetes a meta-analysis of ten studies showed a decrease in hemoglobin A1c of 0.34% and a decrease in fasting blood glucose of about 16.6 mg/dL with chromium supplementation. A study just out in 2013 found no change in hemoglobin A1c although there was a similar drop in fasting blood glucose with chromium use. He felt that it could be tolerated for most patients but not those with kidney disease. Third he discussed cinnamon (Cassia) at 2 grams per day. It decreases lipids and glucose in Type II diabetes and increases insulin action. A 2012 meta-analysis of ten studies lasting 4 to 16 weeks found no significant effect on fasting blood glucose or hemoglobin A1c. On the other hand, there were no significant side effects. He felt that physicians could tolerate its use but would advise against. Fourth he discussed ginseng. It has been shown to increase insulin sensitivity and decrease insulin resistance. A 2011 meta-analysis however found no significant difference in post-prandial blood sugars, fasting blood sugars or hemoglobin A1c. The use of American ginseng (which apparently is a different type) at 1 to 3 grams 40 minutes before a meal did lower the post-prandial glucose by 9 to 13%. He said therefore he would tolerate the use of American ginseng but not regular ginseng. He did mention, however, that there may be estrogenic effect and it may lead to insomnia. Fifth he talked about apple cider vinegar. This is fermented apple juice. The acidic acid slows down carbohydrate breakdown. One study showed a decrease in post-prandial blood sugar while another showed a decrease in fasting blood glucose. It is usually well tolerated but he recommended not using the tablets. He felt he could make no conclusion at this time. Sixth he talked about coenzyme Q10. It is a fat soluble enzyme that has antioxidant effects. A small study over 12 weeks showed a decrease in hemoglobin A1c of 0.37% and also led to a modest decrease in blood pressure. Other studies showed no change in hemoglobin A1c level. He wonders if it might benefit those on statins. Finally he mentioned fenugreek, gymma, prickly pear cactus and magnesium. He really could not comment on their use. There were two other talks on omega-3 compounds and vitamin D. They had no real bearing on children nor on Type I diabetes. It was mentioned that the European guidelines recommend eating fish. If eaten once per week there was a 15% decrease in coronary heart disease and if eaten two to four times per week there was an 18% risk. If eaten once per week, coronary heart disease mortality dropped 36%. It also may decrease the death rate in patients on ACE inhibitors. (*Thus I would highly recommend that we eat more fish to get the omega-3 effect.*)

Teens and the Internet

Over lunch on Friday there was a brief session on using the internet to reach teens with diabetes. Margaret Gray, RN presented her views. She felt teens do best when they are active problem solvers. They do not do well with the passive "tell me what to do". Thus they have been working at Yale on coping skills training. They now have a program called Teen Cope that is designed for 11 to 14-year-old diabetics. It is interactive and does not contain a lot of text. They have been testing it along with Children's Hospital of Philadelphia and they have now entered 120 children into the program. They find that there is a significantly better A1c in the patients using this program. It has taken 18 months of development and has cost $200,000. They make sure that there is a monitor to ensure its safety. They are hoping to reach a point where it could be disseminated across the country but currently it is only available to Yale and Philadelphia patients. *If this does become available we will certainly look into it for you. Most of us do not understand effective use of the internet very well and could use whatever help we can get.* They reported that if the A1c was good at the start it would be maintained through the program. This program is not designed for children 10 or less but they could set up a similar program for this age group. They reported falsifying was not an issue since it is not a discussion of the patient's own care or numbers. Thus they can maintain anonymity. It is a five week program with each session lasting approximately one hour and then the patient returns for discussion. When offered later, 55% of the patients went back to utilize it again. She emphasized that it is designed to build coping skills not specifically to improve control.



Psychosocial and Behavior

It would be remiss of me not to have some psychosocial or behavioral health comments from these meetings. I did not go to any of the sessions this year but there were some posters that I wanted to call to your attention. First there was a group from the Bronx, New York that looked at identity development and social support in adolescents with Type I diabetes. Their results "suggest that adolescents consistently perceive Type I diabetes as a significant burden on their daily lives. The majority expressed a desire to feel "normal" but felt their social lives were complicated by the burden of daily Type I diabetes self management, particularly in the social settings". They found that girls were more likely to incorporate the illness into their identities

and as a result have greater acceptance of the diabetes. Boys were more likely to ignore self management regimens and deny the diagnosis of Type I diabetes affected their identities. *This idea of incorporation is appealing to me. I would love to have more of my teenagers be able to incorporate diabetes into their identity and to accept it as just part of their daily routine. Obviously I must be doing something wrong in many cases.* A group from Los Angeles looked at a peer mentoring program to improve adherence in adolescents with diabetes. They stated that peer mentoring has been considered a cost effective tool to improve health in chronic diseases but that there has not been a study to evaluate it as a strategy to enhance adherence in youth with Type I diabetes. They studied a group of adolescents between 13 and 18 years that were paired with a mentor with diabetes in the age group of 19 to 25 years. The patients reported that they favored a combination of group and one-on-one meetings on an ongoing basis. They preferred pairings with mentors in a different life stage than they were. Thus the mentors were in high school, college or post college. Content areas that were included in the program were social and emotional challenges such as feeling different from peers, applying dietary recommendations in real world settings, checking blood glucose as recommended and advice on major transitions such as moving away from home or away from their pediatric providers. The participants viewed the concept favorably and had few concerns about its implementation. *This is an ongoing study and I suspect we will hear more results over the next couple of years. They were just reporting that the idea was appealing to patients this year.* Researchers from the Type I Diabetes Exchange Clinic Registry looked at the effect of attention deficit disorder on diabetes management and glycemic control among adolescents and young adults. They analyzed 4,530 adolescents and young adults between the ages of 13 and 26 years. This was a chart study so they were classified as ADHD not on medication, ADHD on medication and no ADHD. Ten percent of the patients reported a diagnosis of ADHD and 51% of those were taking a medication. They did not specify what medication but I suspect most were on stimulants. The number of blood glucose tests per day was pretty similar in the groups varying from 4.5 in the ADHD not on medication to 5.0 in the no ADHD group. Patients on medication were more likely to report missing insulin doses compared to no ADHD patients (41% versus 30%). The mean hemoglobin A1c was higher in ADHD patients not on meds (9%) but not ADHD patients on meds (8.7%) when compared to the no ADHD patients (8.6%). They also found that the frequency of DKA or severe hypoglycemia was highest in the group of ADHD not on meds. They concluded "ADHD adversely effects diabetes management and clinical outcomes. Type I diabetes outcomes in patients with ADHD, with and without treatment, should be further assessed". *I find these kinds of studies fascinating. We so often concentrate on diabetes management and oftentimes the patient's inability to complete it and forget that there may be attention issues. In their group, 10% of the patients were diagnosed with ADHD. I am curious if there were not more that just had not been diagnosed. We need to keep this in mind and parents need to let us know what their thoughts are when diabetic control is suboptimal. There may be an additional problem than the diabetes alone that is keeping your child from good diabetic control.*

A group from Richmond, Virginia and Washington D.C. looked at family structure and family size and the impact it has on glycemic control in patients with diabetes. They reviewed

257 adolescents at the two different sites. They used a family density ratio which was merely a ratio of number of children in the home to the adults in the home. They determined that a ratio greater than two was considered "higher family density". They found that adolescents in single parent families were in poorer glycemic control with a mean hemoglobin A1c of 9.41% versus 8.65% in patients with a two parent home. They also found that adolescents from higher density families were in poorer control with a mean hemoglobin A1c level of 10.3% versus those from lower density families 8.61%. They concluded that "although single parent families have youths in poorer glycemic control, higher family density appears to be our more potent indicator of youth glycemic control perhaps because it may be a more sensitive indicator of available parental time and resources". *This report certainly has bearing in Utah with higher family density families. I do not know how to get around the problem but we should recognize it as a potential factor in helping our teenagers get through these difficult years with diabetes.* The group from Pittsburgh compared family planning vigilance in adult women with Type I diabetes. They sampled 88 patients who were between 18 and 38 years of age. Only 23% of the patients reported having received preconception counseling and care. The mean age that they became sexually active was 18.5 years. Ninety-nine percent had used some form of birth control but only 55% were vigilant using birth control every time they had sex when not planning a pregnancy. When compared to women who did not use birth control every time, the more vigilant women used condom and hormone combination birth control methods, had a younger age when first receiving preconception counseling (18.3 versus 23.5 years) and were more likely to have discussed preconception counseling with health providers (73% versus 49%). They concluded that women with Type I diabetes avoiding pregnancy should be extra vigilant with birth control but that almost half of their sample were not. They felt that earlier preconception counseling was a definite factor in the women who were practicing vigilance. *This is the same group that has written the book Ready-Girls that I mentioned before. Again, I think we need to make this much more of a topic in our clinic so that we can at least have the girls thinking before they do become sexually active.* A group from Portland, Oregon looked at Skype based family problem solving in adolescents. They used something known as the behavioral family systems therapy for diabetes and delivered it face to face to patients in clinic and via Skype for patients who were not in clinic. They chose only patients with the hemoglobin A1c of greater than 9%. At enrollment, the mean hemoglobin A1c was 11.01% and the duration of diabetes 6.7 years. The mean participant age was 15 years. From baseline to the three month follow-up, the hemoglobin A1c for the clinic group declined by an average of 0.59% while that for the Skype group declined an average of 0.34%. Using the diabetes self management profile they found that the scores increased in the clinic group by an average of 5.91 points while those using Skype increased by an average of 2.97 points. There was no significant difference between the two groups. They concluded "these findings suggest that BFST delivered by video conferencing is equal in effectiveness to traditional BFST delivered in person". *I realize they found no statistical difference but just looking at the numbers there seems to be some difference. The other problem, of course, is that they achieved very little improvement in hemoglobin A1c at the first three month visit. I am not sure that either system was particularly effective. I hope that they are planning to go on another few months so that we can see how it plays out over a longer stretch.*

Finally a group in St. Louis presented a poster entitled "Marriage Can Be Murder; Impact of Spousal Behaviors on A1c in Type I Diabetes". They found that certain behaviors between couples could be associated with better glycemic control. Couples who exercise together had an odds ratio of 3.8 for having a hemoglobin A1c less than 7. Patients who were reminded by their spouse to test their glucose had an odds ratio of 3.5 for having a hemoglobin A1c less than 7. Patients whose spouses encouraged them to make healthy dinner choices had an odds ratio of 4.2. If the spouse was familiar with the insulin regimen, there was an odds ratio of 4.13 for having a hemoglobin A1c less than 7. They concluded "these findings suggest that spousal involvement improves glycemic control in the adult with Type I diabetes". *As some of you know, I have been using this fact for years in clinic with our older teenagers. I encourage girlfriends to come to the clinic visit and use them as an ally. I am amazed at what a good, well informed and motivated girlfriend can do with some of my recalcitrant teenage boys. I am not at all surprised that this carries over into marriage.* So there you have what I found to be of particular interest in behavior health. The READY group from our clinic did not report this year because they were not quite at a stage to present data. I suspect we will hear from them at the meetings next year.

Transition from Pediatric to Adult Care

Moving on to transition between pediatric and adult care providers, I first wanted to mention a study from the Barbara Davis group. They stated "the transition from pediatric to adult diabetes care is a major healthcare issue. It comes at a high risk time for adolescents. The transition often occurs when youth are facing difficult developmental challenges resulting in a significant risk to those with Type I diabetes". They did a retrospective survey of 51 patients who made the transition from pediatric to adult care at the Barbara Davis Center. Remember that the Barbara Davis Center provides care both for children and adults so the patients stayed within the same system and building. The average hemoglobin A1c at the last pediatric appointment was 8.91% and at the first adult diabetes appointment, the average hemoglobin A1c was 9.11%. The average time to transition to adult care was 5.6 months. Interestingly they found that the patients' subsequent hemoglobin A1c levels at the adult care were not significantly different from their pre-transition hemoglobin A1c level (an increase of 0.27%). They concluded "these data indicate youth with Type I diabetes experience worsening diabetes control and elevations in their hemoglobin A1c during the transition to adult care".

Our program is working on a transition clinic that may help ease the burden. Even with the best of care, however, it is still a time where patients oftentimes seek more independence and less parental involvement. Adult care providers deal with the patient and not the family while pediatric providers deal with the family along with the patient. I know in my office when I see transition patients parents initially come for the first year or so and then gradually let the later adolescent take over. This will be a consideration in clinic. The bottom line, however, is that no one has figured out how to do this particularly successfully. The Yale group also looked at 19 patients in the Yale Type I diabetes Bridge Clinic, which is a transition clinic. They tested to see if the worsening control was due to lack of knowledge or some other factor. They used a 20 item quiz to determine the adolescent's fund of knowledge. They found that the knowledge quiz

score did not correlate with the hemoglobin A1c. Patients with quiz scores of greater than 85% were just as likely to have higher hemoglobin A1c's as they were to have lower hemoglobin A1c's. Because it is Yale, you need to note that higher hemoglobin A1c's were greater than 7.5% whereas they defined lower values at less than 7%. They concluded "these data underscore the need for clinicians to carefully assess other factors that may impede glycemic control during the transition process, such as diabetes distress/burden of care, fear of hypoglycemia, depression disordered eating and to develop better motivational strategies for patients with Type I diabetes during the transition process". *I firmly support what they are saying. Our experience is that the patients know their diabetes very well. It is just that they do not choose or are unable to utilize that knowledge.* The Barbara Davis Center in conjunction with the group from Portland looked at conversations that went on during transition between the adolescent and the care provider. They noted that the 2001 ADA position statement recommended discussing psychosocial issues, mental health, complications and sexuality. They had an after visit form that looked at what was in fact discussed. The topics the adolescents most frequently reported were physical activity (72.4%), supplies/refills (67.2%), meal planning (39.7%) and complications (39.7%). The providers reported the most frequent topics to be physical activity (64.3%), supplies/refills (39.0%), support (38.1%) and driving (38.1%). The topics that the youth reported discussing the least were anxiety (3.4%), pregnancy (5.2%), sexuality (6.9%), depression (8.6%) and diabetes burnout (8.6%). The providers reported the topics least discussed were work (2.4%), career (2.4%), sexuality (2.4%), ADHD (2.4%) and pregnancy (2.4%). They concluded "further investigation is needed in this area including resources to assist providers with tackling the critical health care issues during transition of care, especially mental health and high risk behaviors". *I suspect if we use the same questionnaire in our clinic we would find almost exactly the same results, partly because to cover all of these topics would require an hour to two hour visit. We do need to keep this in mind during transition, however. Perhaps this could be a focus of our educators in their assessment visits. Oftentimes diabetes knowledge is not an issue but these other factors are very much an issue.*

Engineering a Beta Cell-A Roadmap

I saved these last two sections to the end not because I do not think they will be of interest, I am sure they will be, but because I am very much out of my league and my mad note

taking will be woefully incomplete. I will apologize in advance for confusion that I am sure I will arouse. The first session was Tuesday morning. It was entitled “Engineering a Beta Cell-A Roadmap”. First Laurence Chan talked about gene therapy-mediated induction of islet neogenesis reverses Type I diabetes. I took copious notes and most of them no longer make sense but here goes. Most of these studies were mouse models. They used gene therapy in liver cells. This is called a trans-genetic process. The current problems are 1) the glucose sensing mechanism, 2) proinsulin processing, 3) timing (many of these cells are two or three hours out of sync with what a normal beta cell would do) and 4) the need for regulated exocytosis. It leads to the induction of beta cell formation in the liver by delivering transcription factors to liver cells. However it also produces exocrine cells that can lead to hepatitis. The treatment has reversed diabetes in some of these mice. When they use Ngn3-Btc they can achieve normalization of glucose in one to two weeks. It lasts approximately two months when Ngn3 alone is used and a lifetime when Btc is added. Interestingly it is true normalization of glucose and there is no hypoglycemia. The question is what the origin of the newly formed cells is. Whatever they are, they produce periportal neoislets that have relatively well formed islet structures. It can also produce glucagon, somatostatin and pancreatic poly peptide which are other hormones that the pancreas produces. It may be that these are adult stem cells in the liver that are shifting to pancreatic production. They have the complete cascade of transcription factors in the beta cells and the same secretory granules as seen in regular beta cells. The question is if they may be sensitive to the autoimmune process because if that is the case they will be destroyed and it will fail to reverse Type I diabetes. One possible mechanism that might work is the beta cell production of T-cell inhibitor (PD-L1) that actually allows 70 to 80% of the mice to return to normal glucose homeostasis. It prevents local T-cell infiltration but does not cause global immunosuppression. Therefore this may circumvent the autoimmunity. Dr. Paul Gadue talked about generation and regeneration of beta cells. He said work has been done with endodermal progenitor stem cells and with pluripotent stem cells. They can be expanded in vitro (in the lab) and can be made to differentiate into many different cell types. The embryonic stem cells are transformed to partly early progenitor cells which then become later progenitor cells and then mature functioning cells. The embryonic stem cells initially become endoderm and then pancreas and then endocrine beta cells. They are trying to stop the process at the pancreas cell level before transplantation. After several months these cells then produce beta cells. He likened it to induction in an embryo. He emphasized they need to start from undifferentiated cells and they need to be devoid of all other cells because if they induce growth it could produce a tumor known as a teratoma. With the cells produced from the endodermal progenitor cells that appear to be beta cells they can produce insulin but no glucagon. In mice, they get a nice induction of insulin release in the same time frame as a normal beta cell. Unfortunately it only produces about 20% of the insulin amount as seen in normal beta cells. With in vivo studies with mice some of the transplants have survived. They do produce a low level of C-peptide (a marker of insulin production). With progressive generations the poly-hormonal cells (that can produce insulin and glucagon) become mono-hormonal. Once the cells have differentiated to beta cells they can no longer grow. Thus there is no new generation of beta cell. Dr. Qiao Zhou talked about regenerating beta cells. The regeneration is from acinar cells and they are reprogrammed to produce pancreatic endocrine cells. It takes about ten days in vitro and about

30 to 40% of the cells are converted. They appear to be real beta cells. The induced cells can normalize hyperglycemia. It takes about two months so therefore it takes a long time to gain maturity. Formation of the islet cells requires enervation but he is uncertain which nerves are involved. Somehow they can retain a stable state. He also pointed out that the GI tract has approximately 12 enteral endocrine cell types. These do not usually make insulin in nature but with induction they can produce insulin within three days. The cells in the duodenum, ileum and colon can be converted and they are very comparable to pancreas cells. He is also looking at the liver as a source of progenitor cells. *That is what I have and I realize it is all mush. I think the bottom line is that they are doing a great deal of work both in the laboratory and in the mouse in trying to either regenerate beta cells or transform stem cells into functioning beta cells. Obviously they have a long way to go (and I have a long way to learn) but my take home feeling was that they feel that they have made sufficient progress that this could be a very viable option eventually. I have no clue when" eventually" would be but I do not think they know right now either. I apologize for being so confused but this is not my field and when they talk they are talking primarily to other researchers.*

Transplantation

The last section I want to talk about (and appear foolish) was a section on transplant therapies for Type I diabetes. Again these were mostly surgeons speaking to other surgeons and they forgot that I was in the audience. First Jon Odorico talked about pancreas transplants-current outcomes and indications. He said that there are expanding indications for pancreas transplants but the two most common are uremia (kidney failure) and hypoglycemia unresponsiveness. There have been 800 simultaneous pancreas kidney transplants, 200 pancreas after kidney transplant and 50 pancreas transplant alone. Eighty percent of the patients on the waiting list have Type I diabetes where the rest have Type II diabetes or other indications. He reported that patient survival is 85% at five years with a pancreas survival of 70% at five years at UCLA. These numbers are better than most centers across the country. One of the important aspects is the donor selection. The older and heavier the donor, the greater the graft loss. If a donor is over 50 years of age there is a significantly worse survival rate as there is if the donor has a larger BMI (is obese). They now do a hemoglobin A1c on the donor to help determine if he or she would be useful. They think that if the donor's A1c is 6 to 7% it is not ideal. He said nowadays there are fewer pancreases recovered and fewer transplanted than earlier. If you look at pancreas function, 80% of the simultaneous pancreas kidney transplants have some function at two years whereas 70% of the pancreas after kidney and 65% of the pancreas transplant alone have function at two years. He says the results are better now because of fewer early technical failures. There is a 5% immunological graft loss at one year. Interestingly with the combined pancreas kidney transplants it is easier to determine the type of rejection because they can do kidney biopsies. The improvement is also due to better immunosuppressive drugs. They use something called quadruple therapy and they have tried to avoid steroids as much as possible. Another interesting point was that when a pancreas is transplanted along with the kidney, it may prolong the kidney transplant survival since the patient will have better metabolic control with functioning beta cells. When they transplant islet cells after a kidney transplant the criteria for

selection are 1) the patient must be 18 to 68 years of age, 2) they have had Type I diabetes for greater than 15 years, 3) they are at least three months post-renal transplant and 4) they have severe hypoglycemia unawareness or severe lability in blood sugar values. The patient can receive up to three infusions of beta cells over eight months. The goal is insulin independence where the patient does not need to use insulin. Ideally the A1c should be less than 6.5% and a fasting blood glucose of 140 or less. She reported that at 75 days post-transplant, 23.5% of the patients are insulin independent. At one year 50% are insulin independent. The reason that there is a better percentage at one year is that many of these patients have received a second or third infusion. For patients that are not insulin independent, the average insulin dose is 0.5 U/k/day (remember most of you are on close to 1 U/k/day). They can document c-peptide production improvement up to one year after the transplant.

Dr. Kevin D'amour talked about stem cell approaches to beta cell replacement. He emphasized that this is necessary due to the shortage of cells available. There are far too many patients waiting for a donor for long periods. He talked about the pancreatic endodermal cell product. These are encapsulated and mature over four months. The advantage here is that it is a renewable source since they are using human embryonic cells. The progenitor cell has beta cell potential. They can generate over one thousand fold in two weeks and going from ten million to billions in just two weeks. The cells can also be cryopreserved (frozen) for up to two years. The delivery system needs to be biocompatible, biostable, able to exclude host cells (antibodies can enter) and retains the grafted cells. The host tissue develops a fibrous capsule which helps protect the cells. At two to three months in vitro, 85 to 95% of the cells have converted to endocrine cells with half producing insulin and half producing glucagon and somatostatin. The other 5 to 10% of the cells become ductile. In mice, the c-peptide starts to increase at 5 weeks and is very stable after 13 weeks. For this study they were stable for the next five months. There was no evidence of hypoglycemia and no evidence of tumogenicity. He stated that a human trial will hopefully be started in the second quarter of next year. They will try to do this without any immunosuppression. Finally Dr. Andrew Posselt talked about novel immunomodulation strategies for transplantation in Type I diabetes. He pointed out with islet cell transplants in the 1990s, 14% were insulin free one year after transplant. After the Edmonton group showed the deleterious effect of steroids, this number increased to 87%. Now 10% of the patients are insulin free at four to five years. The main problem is the autoimmune rejection. With thyroglobulin Entacept, 50% of the patients are insulin free at five years. However there is significant toxicity. He talked about several different drugs that I know nothing about, saying that they are being tested and some of them rejected due to toxicity. My impression, however, was that there are newer and better drugs slowly appearing on the market.

So here you have the third arm of the potential "cure" for diabetes. First we have the artificial pancreas which is really not a cure per se but replaces what the patient no longer can do. It sounds as though this will probably be the earliest form available to our patients. Obviously there will be considerable expense and a good deal of experimentation when it reaches the stage of being viable on an outpatient basis. It took years for pump therapy to be considered safe and standard. It will take several years for continuous glucose monitoring to be

considered advantageous and accurate (although safety is less of a concern). Ultimately these two will be combined and I think that this will be the first approach at cure. The second is transplantation. They have been doing transplantation for many years but they are now getting closer and closer to having sufficient beta cells that we would be able to supply the need and having safer regimens that do not leave the patient vulnerable via immunosuppression. This approach may well be a "cure" in years to come. They still have a ways to go but my impression is they are making progress. The third is use of the stem cells. Here again I know very little about it and it sounded as though they still have many obstacles to overcome. Nevertheless they do seem to be making progress. The take home message as far as I am concerned is that each of these arms is being explored extensively and seems to be making progress. Surely one of them will prove to be beneficial to our patients and enable them to lead healthier and safer lives. I guess this means that I am deep at heart an optimist in that I truly believe one of these arms will be available in the not-too-distant future for many of my patients. I am sure I will not be in practice at that point but I will be very pleased for all of you.

So there you have my summary for this year. I am hoping that this is much smaller than the ones from the last few years but once you put me in front of a dictaphone I lose track of time and distance. I hope that some of these thoughts are useful. They certainly help me crystallize my thoughts to some degree. Obviously some of the latter sections merely confused me even more. Next year the meetings are in San Francisco and I hope I will be able to report on a baseball game for you. The weather certainly will be nicer. However, I was in Chicago when the Black Hawks won the Stanley Cup. The city celebrated and that was fun. Until next year.