Preliminary Trip Report – 5th Annual Diabetes Technology Meeting (Draft)
November 11 &12, 2005
San Francisco Airport Hyatt Regency Hotel

I was very impressed 5 year ago when I attended the first Diabetes Technology Meeting. What makes this meeting unique is the way in which industrial, academic and clinical topics are blended into a cohesive whole. The mix of attendees reflects this variety providing multiple of perspectives on diabetes care technology. One thing that is different this year is that the meeting is more international. It seemed like about 1/3 of the attendees and presenters were from outside of the U.S.

Some General Conclusions Based on the Presentations

The inherent time lags in plasma glucose concentration sensing and insulin distribution appear to be a major barrier to developing closed loop control of plasma glucose concentration. This is particularly true after meals (postprandial). It appears that to obtain tight regulation of plasma glucose concentration some type of feed forward control must be used. Current techniques require some action of the part of the patient (injecting insulin, pushing a button, etc.) to achieve this. A possible alternative would be to sense changes in GI hormone levels or GI electrical activity.

Specific Presentation on Friday, November 11

Disclaimer and Note to Students: My comments regarding the presentations are intentionally brief summaries intended mainly for my students at MSOE. I am generally not an expert in the topics discussed. Contact the named speakers for clarifications and details. Freshmen should be able to understand parts of the following descriptions. Seniors should understand large portions of them.

The first session covered technologies for metabolic monitoring. Michael Engelgau, M.D. of the Centers for Disease Control opened the session with a summary of the scope of the diabetes problem. In particular, he pointed out that over 20 million American now have some form of diabetes (see the 2005 Diabetes Fact Sheet (http://www.cdc.gov/diabetes/pubs/factsheet05.htm) for more information). He did point out that while the number of people with diabetes is increasing the rates at which they are experiencing serious consequences from their disease is starting to decrease as a result of improved diagnosis and treatment.

The keynote address was provided by Jeffrey Sutton, M.D., Ph.D. of the National Space Biomedical Research Institute (NSBRI, http://www.nsbri.org/). He talked about his institute's involvement in evaluating and mitigated the health risks associated with space flight (glucose monitoring and islet cell cultures are of great interest to NASA). He mentioned some of the physical problems with space medicine and showed a video clip of a physician astronaut trying to take a blood sample during a hyperbolic zero g flight (clips from the video can be found on the NSBRI website). He also described some recent discoveries regarding blue light receptors in the eyes that seem to help regulate circadian

rhythms (see http://www.nsbri.org/Research/Projects/viewsummary.epl?pid=159). He also noted that bone and muscle lose continues to be a problem during long term space flight.

Mihailo V. Rebec, Ph.D. of Bayer Diagnostics was the next speaker. He talked about characterizing the time lag in continuous transdermal glucose monitoring (time lag was mentioned in a number of the day's presentations). He described a device that is still in the R&D stage of development but progressing rapidly towards clinical trials. He used the Parkes Error Grid (see Diabetes Care 23:1143-8; 2000) which is related to the Clarke Error Grid (see Diabetes Care 10:622-628; 1987 and Diabetes Technology & Therapeutics 7:776-9; 2005). These grids are commonly used to evaluate the performance of glucose monitoring devices by classifying the seriousness of the errors in their measurement. He compared his device to the GlucoWatch (http://www.glucowatch.com/us/default.html) and the MiniMed Gold (http://www.minimed.com/products/cgms/). He used a compartmental model in the analysis of his device.

The next speaker was Philip Stout, M.S. from LifeScan (http://www.lifescan.com). He described his work on measuring glucose in interstitial fluid (ISF) sample and how these measurements relate to blood (or plasma) glucose concentrations. As you would expect, there is a time lag. He used the Parkes Grid, but also talked about the correlation coefficient, R.

Marwood Ediger, PhD. of VeraLight (http://www.veralight.com/) then described his company's skin fluorescence spectroscopy (glucose reacts with a number of biomolecules to produce fluorescent compounds) based device. The device is in early clinical trials and is intended for type II diabetes screening applications. He used the term diabesity describe the combination of diabetes and obesity. He stated that 1 in 3 babies born today in the U.S. are expected to have diabetes in their lives. He indicated that the common fasting glucose test appear to miss about half the cases of Type II diabetes.

The last speaker in this session was Volker Lodwig, Ph.D. of the Institute for Medical Informatics and Biostatistics in Basel, Switzerland described the ROSSO Study. This study involved evaluating the impact of self monitoring of blood glucose (SMBG) concentration in type II diabetics. It followed Good Clinical Practice (GCP) guidelines and included about 3000 patients and 6 years of data. The analysis included a COX regression and determination of hazard ratios. The conclusion was that SMBG reduced non-fatal complications by 32% and fatal complications by 50%. This was in spite of the SMBG group patient having higher initial and final HbA1c (the standard measure of long-term average plasma glucose concentrations) levels.

The next session covered the detection and impact of recurrent hypoglycemia (RH) on the central nervous system (CNS). The first speaker was Rober Shewin, M.D. of Yale University who describe the effect of brain ISF glucose. He first described metabolism in CNS neurons which is more complex that I had realized. Neurons apparently derive a substantial portion of their energy from lactate provided by nearby astrocytes. He noted

that brain ISF glucose concentrations are only about 30% of those in plasma and that brain ISF lactate concentrations are higher than glucose concentrations. He described both human and animal experiments. In the animal experiments, he found that rats exposed to RH once a month out performed control rats when tested in maze when euglycemic and this difference improved as the rate aged (yes, this is counter-intuitive, but may be consistent with observation that rats on very low calorie diets live longer than rats given free access to food and high glucose concentrations are associated with accelerated aging like changes in cells and tissues).

Brian Frier, M.D. of the Royal Infirmary of Edinburgh spoke next about the consequences of recurrent hypoglycemia in type I diabetes. He described the prevalence of hypoglycemic episodes in type I diabetics. He noted that low HbA1c levels corresponded with impaired awareness of hypoglycemia. This was apparently the result of adaptive changes that occur in the brain after RH. It appears that tight (or strict) control of plasma glucose (that is known to reduce the risk of serious long-term consequences in type I diabetics), increases the risk of impaired hypoglycemia awareness (also referred to as hypoglycemia unawareness).

The next speaker was Anthony McCall, M.D., Ph.D. of the University of Virginia who spoke about hypoglycemia unawareness and prediction episodes of hypoglycemia. He describe a non-linear transfer of the blood glucose (BG) concentration that provided a Gaussian like distribution of ill effects (both hypo and hyper glycemia cause problems, but in an asymmetric way relative to normal plasma glucose concentrations or about 90 mg/dl (5.0 mM)). He also described High Blood Glucose Index (HBGI) and Low Blood Glucose Index (LBGI) that have been found to be useful in predicting impending hyper and hypo glycemic episodes, respectively. He described who islet cell transplants can reduce the variability in BG values and the risk of hypoglycemia even when the recipients continue to require injected insulin.

Nejhdeh Ghevondian of AiMedics (http://www.aimedics.com/index.htm) in Sydney, Australia was the last speaker in the session. He described the HypoMon® system, a neural network based approached to identify hypoglycemia. The method uses heart rate, QT interval and skin impendence. He described glucose clamp experiments (involving infusion of insulin and/or glucose) in humans. The method he described would probably only be useful for overnight use, but according to several of the previous speakers overnight hypoglycemia is common problem.

The next session covered artificial pancreases (none of the presentations describe implantable or fully closed loop devices). The first speaker was Martin Ellmerer, Ph.D. of the Medical University of Graz in Austria. He described the CLINICIP partnership (http://www.clinicip.org/). The goal of this group is to is to significantly improve survival chances of patients in intensive care units (ICU) using closed loop insulin infusion. It has been found that tight glycemic control (80 to 100 mg/dl) in the ICU is of significant benefit to patients. Previous approaches to this control were manual and complex and did not provide particularly good control. The CLINICIP system is more automated (the current version involve manual plasma glucose measurement, but the inclusion of

continuous glucose monitoring is planned as soon as a sufficiently accurate and reliable technology becomes available). Monitoring of patient nutrition (IV and enteric) has been found to be critical to successful glycemic control. The current system uses patient specific linear models in its control algorithm.

Tim Goodnow, Ph.D. of Abbott Diabetes Care (http://abbottdiabetescare.com/) spoke next. He described his company's Freestyle Navigator continuous glucose monitoring system. The device is currently in the PMA stage of development with clinical trials about to start. It use a polymer/osmium based glucose oxidase based electrode that does not exhibit any dependence on O_2 or H_2O_2 concentrations. The electrode is inserted subcutaneously using a special applicator and held in place with adhesive. It has a 5 day working life span and must be calibrated using standard test strip measurements (at 10, 12, 24 and 72 hours after insertion).

The next speaker was Thomas Vering, Ph.D. of Disetronic Medical Systems (http://www.disetronic.com/disetronic.asp?menuId=2&languageId=2) in Burddorf, Switzerland the makers of Accu-Chek brand products. He described a closed loop insulin infusion system consisting of an insulin pump connected to a controller that monitors ISF glucose concentration using a microdialysis sampling system. He described the results of two clinical trails using the device. He described the control algorithm as a simple adaptive feed back system with a feed forward component. The feed forward component is required to provide adequate control after meals.

The last speaker in the session was Moshe Phillip, M.D. of Tel Aviv University in Israel. He describe the results of clinical trials with the MiniMed Guardian RT (http://www.minimed.com/products/guardianrt/) continuous glucose monitoring system. He noted that weight gain and increased frequency of hypoglycemic episodes have been associated with tight glucose regulation. The Guardian system involves a 3 day sensor requiring calibration twice a day. He noted that, relative to a control group, the use of the new device resulted in lower HbA1c levels in patients with fewer hypoglycemic episodes.

Friday Night Poster Session

There were too many interesting posters to describe each in detail. A number were related to glucose concentration measurement. They're based on technologies like IR, UV and even visible light (with the help of implanted dyes) spectroscopy, fluorescence, electrical impendence, acoustic resonance, several types of electrodes, direct sampling, dialysate sampling even holographic techniques. Others posters dealt with insulin delivery (including "smart" insulin that "delivers" itself when needed) and modeling and control techniques. I finely found out what "coding" that is mentioned on glucose monitoring ads is (it's the entry of a calibration code to correct for variability between different lots of test strips). I collected some literature at the poster session to place in S-327 for student use.

Specific Presentations on Saturday, November 12

Today's first session covered insulin delivery technologies. The first speaker was Gordon Weir, M.D. from Harvard. He described the current state of islet cell transplants (the alternative is to transplant entire pancreases). Such transplants have met with reasonable success since about 2000. In the Boston program, 18 of the 34 patients they have treated were off insulin for at least a while. Issues with these transplants include the typical need for two or more donors (to make up for cell loses in the processing of the organs) and most patients need insulin after two years (but continue to benefit from the procedure in that their blood glucose concentrations are more stable. Other problems include possible side effects of the anti-rejection drugs needed by the patients (including possible kidney damage). Whole organ transplants generally give better results, but cell transplants can make use of inferior organs. Alternative sources of cells are needed. Suggested sources include embryonic and adult stem cells, β cell expansion (replication in culture), β cell differentiation from progenitor and duct cells (which appear to be possible in cell culture) and genetically engineered cells (involving multiple viruses carrying multiple genes and involving selection and screening), in vivo regeneration of β cells, xeno-transplant (porcine) and encapsulated cells.

Mathew Riddle, M.D. of the Oregon Health & Science University next talked about various insulin analogues (insulin with one or two changes in its primary sequence) and other issues associated with diabetes treatment. He noted the positive outcome of a 22 year study in which the best possible glucose control strategies were used. He felt future improvements in care will likely involve inhaled insulin (that is nearing FDA approval), closed loop control (even short term 2 or 3 day duration use would be beneficial) and combining insulin with amylin (which is secreted by the β cells) and GI peptide hormones (like GLP).

The next speaker was Simon Lawton, M.D. of Novo Nordisk (http://www.novonordisk.com/) in Denmark (there were a large number of Danes at the conference) talked about the rapid acting insulin preparations that are used in insulin infusion pumps. He described issues related to their physical and chemical stability and local tissue responses to them. He noted that insulin exists in a dimer and hexamer state in the preparations. He noted that precipitation can occur if the preparation pH drops too low and insulin fibers can form irreversible if the insulin molecules partially unfolds (often as the result of excessive heat, shearing or contact with hydrophobic solutions). He described the common additives used in insulin preparations and their functions. These include zinc ions, phenolic acid and surfactants. He presented data indicating different stability and local toxicity performances of different preparations.

Andrea Leone-Bay, Ph.D. of MannKind Corporation (http://www.mannkindcorp.com/about_us/index.cfm) next described a very interesting inhaled insulin product being developed by her company. It involves adsorbing insulin onto self-assembling nano-spheres ("Techospheres®") of a unique organic molecule. The spheres are formed by precipitation from an aqueous solution in response to a change in pH. She noted that in order for microspheres to enter the deep lung (where rapid absorption can take place) the must between 0.5 and 5.8 μm in diameters. Their spheres

are mostly within this size range. The spheres are very porous and have very high surface areas. They dissolve on contact with water at physiologic pH. She also noted that normal insulin secretion after a meal is a two phase process involving both feed forward and feed back mechanisms. Type II diabetics generally lose the first phase of this response and their product is intended to be used just prior to a meal to simulate the first phase of this response. They have demonstrated the feasibility of their product in initial human trials. In these trials they not observe any increase in insulin antibodies (a major concern with inhaled insulin because the lungs have a particularly strong immune response). The FDA classifies their sphere material (FDAP?) as a new material and is requiring extensive biocompatibility and safety testing.

The next session covered nanotechnology applications to diabetes treatment. Most of the material presented in this session described work in very early stages (research as opposed to development). The first speaker was Michael Strano, Ph.D. of the University of Illinois. He described a carbon nanotube based approach for measuring glucose concentration. He noted that nanotubes can be made to fluoresce in the near IR where tissues are relatively transparent and are not subject to photo-bleaching like ordinary fluorescent dyes. He described an approach in which glucose oxidase (GOX, a.k.a., GOD) is immobilized on the nanotubes and redox coupled to them. The nanotubes are then enclosed in micro-dialysis tubes to form a flux based sensor. After describing a flux based sensor, he made the distinction between affinity and flux based approaches and noted that affinity sensors are less subject to drift caused by biofouling. He stated that his lab is working absorption isotherm based affinity sensor also based on the carbon nanotubes. Finally he claimed his fundamental approaches are very versatile and could be used to measure concentration of a number of materials.

Michael McShane, Ph.D. next spoke about “smart tattoos” (particles that respond to changes in glucose concentration in a way that can be monitored transcutaneously) involving particles coated with nanolayers of polymers. He discussed general system requirement and described an approach to forming the nanolayers involving alternating layers of positively and negatively changed layers. The model system he described involve GOX. The particular system he described involved entrapping the GOX and an oxygen sensitive fluorophore in alginate spheres and coating the spheres with nanolayers to limit glucose and oxygen transport. He described a mathematical model of the system that involved coupled partial differential equations (PDE’s and a subject near and dear to me). The model was apparently implemented in Matlab and used to find the optimal sphere diameter and layer thickness. Finally he described an alternative competitive binding approach that would provide concentration rather than flux based results.

The last speaker in this session was Shirley X. Y. Wu, Ph.D. of the University of Toronto. She spoke about her work in developing a nanoparticle based insulin delivery system that would automatically respond to changes in glucose concentration. Her approach involves making nanoparticles from a copolymer of temperature and pH responsive hydrogel monomers. By changing the ratio of the monomers, polymers can be produced that under a dramatic volume change at specific pH at body temperature. The nanoparticles are then incorporated into macroparticles. The combination produces a

material with pores that open and close based in response to pH changes. This material is then saturated with insulin and GOX. In the presence of high glucose concentrations, the gluconic acid formed by the GOX lowers the pH in the macroparticles resulting in the collapse of the nanoparticles and an open of the pores in the structure. This in turn allows release of insulin. The process is reversible and she showed data involving repeatable insulin release over three cycles.

The third session of the day was entitled "Computers and Diabetes." The first speaker was Irl Hirsch, M.D. of the University of Washington. Dr. Hirsch is a particularly engaging and enthusiastic speaker. He described the clinical value of having his patients upload their glucose meter data for analysis. He noted that high standard deviations in the concentration data are associated with increased oxidative stress. He uses an electronic medial record (EMR) systems made by NuMedics (www.numedics.com).

Michael Engelgau, M.D. of the Centers for Disease Control next spoke about computer disease modeling. He noted that most clinical trials don't last long enough to provide data for making health policy decisions involving chronic diseases. He suggested the use of computer models can provide alternatives to complex, long-term studies. He explained that there are at least two types of models. Markov (state based models) with non-time dependent state change probabilities and more complex object oriented models that involve the simultaneous solution of systems of ordinary differential equations. Model parameters generally involve transition probabilities, resource utilization and cost estimates and quality of life scores. He then described how such models can be used to aid in making health policy decisions.

The next speaker was Eldon Lehann, M.D. of Imperial College in London. He described blood glucose concentration simulation for diabetes education. He spoke in general about how the value of software can be investigated. The particular model he described is call AIDA is available from www.2aida.org. He described a randomized, controlled clinical trial that showed the use of the simulation for patient education resulted in significantly lower HbA1values and the frequency of hypoglycemic episodes.

Echard Salzieder, M.D. of the Institute of Diabetes in Karlsburg, Germany next described his experience with the KADIS® model (an expert system?). He noted that data from a continuous glucose monitoring system is necessary to use the model for patient specific decision support. He described a clinical trial in which the use of the model for case management resulted in significant reductions in HbA1c, mean blood glucose concentration and insulin requirements.

The final speaker of the session was Jae-Hyoung Cho, M.D. of the Catholic University of Korea in Seoul. He described two very cool telemedicine systems. The first system they developed involved patients using home computer and the internet to upload the glucose meter reading and advice from their health care providers. While this system was shown in clinical trials to help lower HbA1c levels relative to conventional care, it was limited in that it was not widely available (it required the patients have access to their computers), it was not real-time and it was costly in term of staffing requirements. The

second system they developed attempted to mitigate some of these problems. It involved the use of a cell phone base glucose meter with real-time voice and text messaging capabilities. The second system was found to provide HbA1c levels as good as those of the internet based system with increase patient satisfaction. He suggested that the phone based system could be improved by including an automatic expert system response capability to provide real-time feedback with a reduced staffing requirement. He also suggested the inclusion a physical activity monitoring system to provide even more information for the calculation of insulin doses. His goal is to provide an ubiquitous medical care system with the clinic as its hub.

The final session of the meeting included an interactive survey and discussion. Multiple choice questions were posted on the screens and the audience asked to respond them using hand-held wireless devices. The survey results for each question were then discussed by the panel of experts with questions and comments from the audience. It proved to be both an interesting and entertaining session.

The conclusions in this session included: tight control of blood glucose (BG) concentrations in hospital patients is coming; in the future BG will be considered a vital sign; most members of the audience expect a functional artificial pancreas to be developed within 10 years and for Type I diabetes to be cured within 25 years; within 5 years telemedicine will like to play an important role in special situations but will not be used universally. The need for an Artificially Intelligence (AI) would be useful to help reduce physician and staff work loads was raised. The audience felt that most funding for diabetes technology develop will come for industry (I got the impression that panelists and attendee felt that spending is a limiting factor in the rate of development of new diabetes technologies).

Saturday Lunch

I had lunch on Saturday with Gregory Loney of Rosendale Medical and Raj Mandavilli of BioSentient Corporation (http://www.biosentient.com/). Both companies are small startup firms. I asked them both what traits and abilities the look for in engineers. They indicated that in addition to strong technical ability and a willingness to work hard (that are givens), the look for the ability to work independent, make good decisions and the ability to work effectively as part of a team. With respect to decision making, it is important to be able to make choices based on the specific situation (company priorities). With respect to being part of a team, it is important to negotiate and be diplomatic.

Some Miscellaneous Comments Regarding the Meeting and Presentations

Some quotes from the session included “no one here is as smart as a β cell,” “we’re overwhelmed and there’s no reimbursement” and “biology is an existence proof of the utility of nanotechnology.”

Many of the slide shows include one or two animated slides. About half the posters were single-sheet (large format printed) and many were laminated (I would have expected

nearly all of them to have been). In the past 5 years: progress in developing continuous glucose monitoring (both implanted and transcutaneous) has been slower than I expected (this technology is needed for the development of “artificial pancreas” (that I define as a device that will continuously monitor plasma glucose concentrations and infuse insulin under closed loop control)); limited progress has been made with islet cell transplants has been made and inhaled insulin has gone from a new concept to nearing FDA approval. According to an informal survey (a show of hands during one of the sessions), a substantial fraction of the physicians at the meeting use e-mail to communicate with their patients. This is the simplest form of telemedicine.