DIABETES CLOSE UP

Know Your A1C September 2007 • No. 72

From the Editor

Remember your school days? The lazy days of summer would come to an end, you'd drift aimlessly into your first class, and then – bam! – bullets – of reality would start flying.

Welcome to the diabetes world, September 2007. We enjoyed a reasonably quiet end to the summer, but now the news is coming from all corners – from the newest LEAD data (announced this morning) to the latest Avandia trauma to an unprecedented new advertising campaign to impressive data about bariatric surgery. And of course, this is good: news often means progress, breakthroughs, and awareness. Even "negative news," as we've seen with Avandia, is useful if it helps us make better decisions about care.

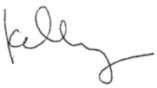
And all the news ensures that DCU bristles with vital information.

This issue we have a super exciting story about the first national diabetes public service campaign, created by the prestigious Ad Council and to be seen or heard on TV, radio, in print, and online. Relying on provocative, edgy messages – not stuffy medical jargon – the ads focus on A1c numbers as a warning signal for future complications. The driving force behind the campaign is the Diabetes Care Coalition, comprised of companies and advocacy groups that haven't always been the closest of friends but have come together for this noble effort. Congratulations to the Diabetes Care Coalition, led by Tom Boyer, for making this happen – and check out YouTube for our take on it - http://www.youtube.com/watch?v=I3qgCzZq0ag.

Meanwhile, Avandia is back in the news, as another study showed that the embattled drug doubled the risk of heart failure and raised the risk of heart attack by 42 percent – but the news wasn't all bad for the TZD class. A second study found that Actos lowered the risk of heart attack, stroke, and death, but, like Avandia, also raised the risk of heart failure.

We're delighted to see that Dr. Steven Edelman's organization, Taking Control of Your Diabetes, will air 12 new half-hour episodes of its television series for broadcast on educational access cable channels through the University of California. This will be the second season of the outstanding show. The first episode appears this Thursday, September 20. (For channel information in your area, check www.tcoyd.org.)

We're now off to Amsterdam to cover EASD, where the big topic will be the 4T data. Mike King of Rodman & Renshaw and I will be hosting a conference call with Dr. Bernie Zinman of University of Toronto and Dr. Jay Skyler of University of Miami so if you'd like to call in, please just send me a message asking for details. The call will be after 4T reports on September 21, before the market opens. As usual, we'll also report on all our findings next month. Yes, summer's over – and going to Amsterdam to learn about all the new research, amidst drinking Dutch beer, will be quite a contrast to pims in San Francisco, which we've been having all summer. Here's to a most excellent start of fall, one and all …



Kelly L. Close

Major Headlines

In This Issue

Blogwatch

Blogwatch - See below for blogs since our last monthly newsletter. You can see any update online at http://www.closeconcerns.com/, or you can subscribe to the RSS blog feed.

- **September 13:** Diabetes to receive unprecedented public attention through Ad Council campaign
- **September 5:** Weighing in on Bariatric Surgery and the NEJM recent reports

Besides writing our own blog, we also write a blog for Revolution Health called "Up Close and Personal" on life with diabetes. You can find it at www.revolutionhealth.com/blogs/kellyclose

- **September 13:** Fabulous new Ad Council campaign jolts us to reality... and action!
- **September 8:** Gestational diabetes and your child's potential obesity - get the best care you can!
- **September 7:** Gestational diabetes and cancer? Uh-oh...
- **August 31:** Baby diet pills?!?
- **August 27**: Dollars for pounds... a diaTribe debate
- **August 27**: Gratuitous DexCom SEVEN post

Videos

Below are our favorite videos in diabetes this month:

- A1C Ad Council Campaign:
  http://www.youtube.com/watch?v=I3qgCzZq0ag
- "Know Your A1C"
  http://www.youtube.com/watch?v=I3qgCzZq0ag
- "NBC Today - Life With Diabetes"
  http://www.youtube.com/watch?v=0AOvhKZUIGY&mode=related&search=
- "Type 1 Diabetes: Calvin's War"
  http://www.youtube.com/watch?v=u9gLg-OyVKY&mode=related&search=
- "JDRF Walk to Cure Diabetes"
  http://www.youtube.com/watch?v=QJbHggAfDKE
- "Prevalence and Cost of Type 2 Diabetes in America"
  http://www.youtube.com/watch?v=Ttl2hDi7d_4

Coming soon in DCU...

We're just gearing up for the 43rd European Association for the Study of Diabetes (EASD) Annual Meeting, held September 18-21 in Amsterdam. The preview for this exciting meeting was in the last issue of *Diabetes Close-Up*. We're also headed to the Cardiometabolic Health Congress on September 26-29 in Boston, MA, and the Cleveland Clinic Obesity Summit on September 27-29. We're literally salivating about all these meetings and trying to find a polite way of saying this. Stay tuned...

1. Quotable Quotes in Diabetes

"Social support is the wonder drug of the twentieth century."
—From our conversation with Neal Kaufman, M.D., M.P.H. (see below), in discussing the basis for founding Diabetes Prevention Source (www.DPSHealth.com), which provides technological solutions to prevent diabetes and cardiovascular disease.

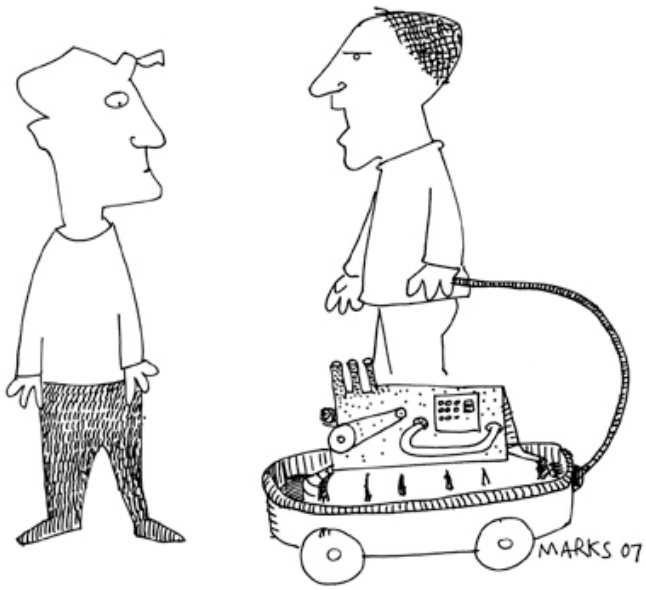
"We are all born with an addiction to sugar, fat, and salt."
—Dr. Kaufman, discussing the challenge in preventing diabetes and cardiovascular disease.

"His position is like being a marriage counselor… We (Amylin and Eli Lilly) have a good marriage. But like every marriage, there are good days and bad days."
—Daniel Bradbury, President and CEO of Amylin Pharmaceuticals, discussing [Amylin exec] John Wood's job managing Amylin's partnership with Eli-Lilly.

"Most physicians will tell you that if you can read the English language, you can operate this product."
—Duane DeSisto, President and CEO of Insulet, speaking about the simplicity of the OmniPod at the Bear Stearns Health Care Conference.

"Regulatory agencies ought to reevaluate whether rosiglitazone should be allowed to remain on the market. Health plans and physicians should not wait for regulatory actions. They should avoid using rosiglitazone in patients with diabetes who are at risk of cardiovascular events, especially since safer treatment alternatives are available."
—Dr. Singh and colleagues, reviewing the implications of their meta-analysis of rosiglitazone published in the September 11 edition of *JAMA*.

2. diaTribe FingerSticks



"I dunno, they said it was a portable medical device…"

-by Benjamin Marks

3. DCU Company Watch

- **Novo Nordisk – 85% of LEAD patient data now in:** Novo Nordisk announced September 14 the fourth of five liraglutide trials. We'll be reporting more on this from EASD, which details results of the 533-patient LEAD trial where patients had a run-in with metformin and Rosi and then liraglutide was added. The average A1c drop of 1.5 % compound to a 8.5% baseline looked impressive although we understand placebo subtracted the change was just 1.0 – weight loss of 2.5 kg was harder to interpret since this was versus placebo but we look forward to learning more. AmIGO trials showed a weight drop of around 2.0, but that was just 16 weeks compared to 26 weeks for liraglutide. Here, as we understand it, the average patient on TZDs gained 2-2.5 kg. There's just one more trial to report, toward the end of this year, so the timing for FDA submission seems well on track – and, Novo Nordisk is at work on a once-weekly version though there is no further news on this front of note at this time. It is going to be terrific to have more marketing of this class from the world's biggest insulin manufacturer.

- **Living Cell Technologies—Approval of phase 1 and phase 2a DiabeCell clinical trial:** Living Cell Technologies announced on September 12 that it received approval from the New Zealand Regional Ethics Committee to initiate a phase 1 and phase 2a clinical trial of its islet transplant product, DiabeCell, in type 1 diabetes patients (n=8). The 12-month trial is expected to begin late this year. DiabeCell is an islet transplant technology in which the transplanted islet cells (in this case derived from pigs) are hidden from the immune system through encapsulation using a proprietary alginate gel. While nutrients and gasses can pass freely through the capsule, the immune system cells cannot enter the capsule, thereby protecting the implanted beta cells. In the clinical trial, the DiabeCell capsules will be inserted into the abdomens of the patients. We look forward to progress in this field, though we note that historically islet transplantation has been a very difficult area in which to show progress.

- **Eli Lilly—Speaking out on multiple diabetes-related fronts:** At the Bear Stearns conference on September 11, Eli Lilly's Sidney Taurel gave an update on the US political landscape as it pertains to the pharmaceutical industry. Referring to the current political climate, Taurel underscored that the new, Democratic majority in Congress has *not* introduced several expected bills that could hurt the pharmaceutical industry – in particular, allowing the government to negotiate drug prices; importation of drugs from Canada (which he attributed to the flawed but convincing argument that the FDA cannot guarantee the safety of these drugs); and revision of patent laws. While he conceded that criticism of the pharmaceutical industry will likely heat up in the coming election, most of the presidential candidates (with one or two exceptions) are not suggesting broad overhaul of the current systems. Taurel remarked that over the past two years, Lilly's sales and growth margins have risen, allowing additional investment in R&D and advertising. These improvements were attributed to improved efficiency – compared to the second quarter of 2004, Lilly has reduced its head count by 5,000 (11%), and sales per employee have risen substantially.

  In Q&A, questions of note included a query on when the FDA will approve the new LAR manufacturing plant; Taurel said the review isn't yet scheduled and that it wouldn't be in the "very short-term." When asked whether Pfizer's Exubera has impacted his views on inhaled insulin, he said yes and moved to point out product differences between Lilly's product in development (AIR insulin) and Exubera. First, he characterized the AIR device as small and easy to use, whereas Exubera is difficult and bulky. He went on to note that Lilly is filing for registration with outcomes data and emphasized that access is extremely important in order to get reimbursement – we certainly had not been aware that at the time of launch, Pfizer did not have those data available. Finally, he stressed Lilly's experience of 80 years: "This is a complex

disease. Our expertise is very important. This will be a competitive advantage. We'll take advantage of having learned from Exubera as well." Lilly did not address commercial issues relating to declining short-acting analog share or the quest for a long-acting insulin analog. We remain extremely optimistic about Lilly's commercial prospects for LAR and are excited for patients to have an alternative way to take exenatide. Although we don't know anything about the first-generation LAR product, we assume it will improve over time. We eagerly anticipate data in the fourth quarter on LAR – and, although unrelated to Lilly, we also look forward to seeing more data on Amylin's INTO (Integrated Neurohormonal Therapy for Obesity) product portfolio, which was introduced for the first time last fall.

- **Arena—Continuing phase 3 BLOOM obesity trial:** Arena announced on September 11 that an independent Echocardiographic Data Safety Monitoring Board (EDSMB) had found no reason to stop its phase 3 Behavioral modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial. The EDSMB confirmed that differences in the rates of FDA-defined valvulopathy in the control group versus lorcaserin-treated group did not meet the predetermined stopping criteria. As a reminder, lorcaserin is Arena's internally discovered drug candidate to treat obesity by stimulating a receptor in the hypothalamus - a part of the brain associated with the control of satiety and metabolism. Dynamics of the current safety climate had prompted concern in at least the eyes of a few that the trial would need to be stopped. The company is currently in the process of finalizing protocols with the FDA for two additional phase 3 trials to evaluate lorcaserin's potential as a safe and effective treatment option for weight loss, said CEO and President Jack Lief. These studies are slated to begin in the next few months

  The double-blind, placebo-controlled phase 3 BLOOM trial enrolled nearly 3,200 patients in 100 centers in the U.S. It will evaluate a twice-daily 10 mg dose of lorcaserin versus placebo over two years in two groups of obese patients:
  - BMI 30-45 with or without co-morbid conditions
  - BMI 27-30 with at least one co-morbid condition

  The primary efficacy endpoint is a 5% or greater weight reduction from baseline at week 52 compared to placebo. The EDSMB reviewed only the six-month echocardiogram data, and we look forward to seeing the results after the 12-, 18-, and 24-month data have been obtained and reviewed. The two additional phase 3 trials scheduled to begin later this year will evaluate 20 mg and 10 mg daily doses versus placebo over a one-year treatment period. One of these trials will evaluate the drug in type 2 diabetes patients, who generally respond less to weight loss treatments than patients with diabetes. Arena has proposed that the FDA continue conducting patient echocardiograms in the two additional studies in light of the Avandia controversy; we are glad to see the company appears to be exhaustively analyzing lorcaserin's safety profile.

- **Amgen—Getting aggressively (back) into diabetes**: CEO Kevin Sharer did not say anything about Amgen's acquisition of Alantos Pharmaceuticals during his discussion at the Bear Stearns conference on September 11 – this was disappointing since we were very eager to find out more about the reason behind buying a clinical stage DPP-4 inhibitor. This $300 million acquisition should close by the end of 3Q07. He spoke about restructuring actions involving voluntary and involuntary head count reductions – this all presumably due to Epo. He predicted 2008 would be a recess year but beyond that, Amgen is looking forward to stronger growth. February 2008 will provide a better vantage point looking ahead. It's striking to us that at a time of pullback, Amgen has set aside funds to invest in diabetes – we have added it to a list of potentially large acquirers moving forward. Responding to a question on why Amgen was developing out-licensing agreements instead of diversifying, Sharer stated that the company had more phase 2 drugs than

it could afford to develop and thus saw partnerships as a positive – this may have implications for diabetes in particular going forward.

- **Medtronic—On fire**: In the words of William Hawkins, new president and CEO of Medtronic, "(Medtronic's) diabetes business is kind of on fire right now." This was a remark during his talk at Bear Stearns on September 11 and, from our perspective, it pretty much sums up the diabetes part of his presentation. Earlier in his presentation, he said that business by business, management was reviewing the company to make sure all franchises were operating at a world-class level. Specifically related to diabetes, he talked about the good traction in Medtronic's continuous glucose monitoring sensor sales, citing ~20% growth for the diabetes business a couple of times. According to our research, this is very true – sensors appear to be currently on back order. Hawkins said he anticipated exciting growth in existing markets and vowed to be opportunistic in adding new products and new markets. Although direct-to-consumer (DTC) advertising is not the mainstay of Medtronic markets, we have been very impressed with recent growth – all the more impressive since none of Medtronic's other businesses have this model, but Medtronic Diabetes is the fastest growing franchise at the company (over 20% per quarter the last two quarters, higher than our already-high expectations).

- **Amylin—Exenatide LAR progress continues:** CEO Dan Bradbury gave a corporate overview of progress at Amylin Pharmaceuticals at the Bear Stearns Health Care Conference on September 10, reviewing progress on exenatide LAR, discussing Byetta and Symlin market growth, and giving an update on the company's obesity program. Bradbury reviewed the phase 2 data on Byetta LAR, which showed a substantial 1.7% A1c reduction from baseline (2.1% placebo) and 4 kg weight loss after 15 weeks. The ongoing phase 3 trial is a 30-week open-label, randomized, non-inferiority study (n=300) against Byetta BID (twice daily) that will be completed in 4Q07. Bradbury explained the mode of action of the drug, giving him an opportunity to mention Amylin's partnership with Alkermes, which supplies some of the technology in the Byetta LAR manufacturing process (LAR is impregnated into microspheres of a Medisorb polymer formulation co-developed by Alkermes, allowing release of the drug over 2-3 months). Alkermes is transferring the necessary technology to the new Amylin facility being built in Ohio at "record pace." He mentioned that the therapy being employed in the phase 3 trial involves layering sub-therapeutic doses in order to ultimately reach therapeutic concentrations of drug. As in the original phase 3 Byetta trials, all patients in the phase 3 LAR study will have the opportunity to go on an extension study to enable data collection on long-term use of the drug. Also in the pipeline is a phase 1 intranasal formulation of exenatide (being co-developed with Nastech).

  Bradbury pointed out that Byetta itself continues to grow, both in clinical applications and in geographic sales. He cited a study looking at the use of Byetta as a first-line monotherapy for patients currently on a diet and exercise regimen. This could represent a potential new market of about 9 million patients (~6 million on metformin and/or SFUs and ~3 million on TZDs). He also noted the February approval of Byetta for room temperature storage and the European launch of Byetta by partner Eli Lilly with great success in the UK, Germany, and Scandinavia. Regarding Symlin, Bradbury noted the expected new indication for use with basal insulin rather than mealtime insulin only, which could double the Symlin market. Amylin expects FDA approval for the indication before the end of 2007. Bradbury admitted that Symlin sales of $44 million last year were modest but expressed optimistic about 2Q07 sales of $15 million. Impressively, there is now universal awareness of Symlin by endocrinologists and increasing awareness among primary care physicians. Bradbury stated that 50% of Symlin prescriptions were from PCPs. With the new pen delivery system expected at the end of 2007 (only two months away) we think that there will continue to be an increase in prescriptions.

Of particular interest to us, Bradbury discussed Amylin's INTO (integrated neurohormonal therapies for obesity) study looking at the use of pramlintide (Symlin) in combination with oral agents sibutramine (Meridia) and phentermine for obesity. We believe some oral agents, such as these two, have higher potential for use in combination therapy than others. The rationale behind combination therapy is that while the side effects of these agents may pose issues when they are given in standard doses, simultaneously administering lower doses of two (or more) agents may create a more acceptable side effect profile. In diet-induced obese rats, pramlintide and leptin, a satiety hormone secreted by fat cells, have been shown to produce synergistic weight loss of 12-13% in 4 weeks compared to 0-2% with leptin alone. An ongoing proof-of-concept clinical study hopes to replicate these results in humans. Amylin is also conducting a safety study on pramlintide and PYY_{3-36}, to be completed this quarter. The success of these studies could open the door for additional multi-combination studies. Bradbury also briefly mentioned that a 2nd generation amylinomimetic optimized for its effect on body weight is currently in phase 1 studies.

- **Metabasis—Disappointing phase 2b trial results for CS-917:** At Bear Stearns on September 11, Dr. Paul Laikind, President and CEO of Metabasis, discussed the company's current diabetes pipeline projects, including CS-917, MD7803 and MB7811. To start, he suggested an explanation for disappointing phase 2b results for CS-917, an orally active type 2 diabetes drug candidate that inhibits an enzyme responsible for glucose production in the liver's gluconeogenesis pathway. Phase 2a trials showed the drug to have good safety and tolerability while significantly reducing elevated blood glucose levels. However, in phase 2b trials completed in July, the drug did not show statistically significant efficacy. Dr. Laikind suggested that the results represented a failed trial and not a failed drug. He pointed to the difference in patient populations used in both trials explaining that the phase 2b trials had newly diagnosed patients for whom gluconeogenesis did not yet play a major role in the disease – hence the lack of efficacy since the drug targets this pathway. We note that while patients with early diabetes can have either impaired fasting glucose (implying liver glucose overproduction) or impaired glucose tolerance (implying peripheral insulin resistance), the latter is indeed a greater contributor to hyperglycemia in the majority of newly diagnosed patients. Nonetheless, we note that metformin, another drug that acts in part on the liver, does effectively lower A1c in newly diagnosed patients. Dr. Laikind described CS-917 as a major market opportunity with potential to be administered alone or in combination with other anti-diabetic drugs, especially for patients unable to take metformin. Daiichi Sankyo has full responsibility for the drug's development program, while Metabasis receives milestones, net sales, royalties, and rights to co-promote in North America.

  Dr. Laikind briefly discussed MD7803, a second-generation version of CS-917 that inhibits the same enzyme and may have potential advantages over its predecessor – i.e. once-a-day vs. twice-a-day delivery. We await the results of the ongoing phase 2 proof-of-concept trial investigating the drug's effect on fasting glucose. Lastly, MB7811 is an orally active first-in-class liver-targeted beta-selective thyroid receptor agonist that possesses a new twist on an old mechanism of action against hyperlipidemia. It is intended for administration as a single agent or in combination with statins to reduce LDL-cholesterol, triglycerides, and liver fat. Metabasis is developing both MD7803 and MB7811 independently. Dr. Laikind briefly mentioned a glucagon antagonist soon to reach clinical development, which Metabasis is developing with Merck; no doubt Merck is looking to expand its diabetes pipeline in light of Januvia's strong performance so far. Metabasis also has an AMP-activated protein kinase for diabetes and hyperlipidemia in early stage and a fourth development stage product of another drug for type 2 diabetes. This will be an interesting pipeline to watch over the next few years.

- **Merck—Januvia and Janumet success a focus at fall conference:** On September 10 at the Bear Stearns Health Care Conference, VP of Marketing Robert McMahon delivered a positive review of Merck's diabetes and obesity business. We were excited to see so much focus on the area and urge readers to download the slides from Merck's site as they illuminate well the rapid changes in type 2 therapy over the past couple of years – namely the rapid emergence of Byetta and Januvia and the downfall of Avandia and the start of a rise to Actos. Barring safety issues, Januvia appears to continue to be on a serious roll – the sales line has taken a sharp turn upward since the Janumet approval in April, and we believe the combo drug, even if it must be taken twice a day, has serious benefits. Specifically, much better A1c reductions (Januvia and metformin do appear to be more synergistic than one might have expected) and a single co-pay are at the top of the list. The Januvia franchise also appears to be benefiting greatly from Avandia's downfall. McMahon noted that Merck's Januvia franchise is currently the third most widely prescribed product in the oral diabetes market – 3.5% of market share in less than one year is extremely impressive though of course its staying power will be what it is ultimately judged by! Actos leads this category with 11.5% followed by Avandia with 4.5% - the latter has dropped precipitously since the Nissen trauma while Actos has increased about a point. We actually believe doctors may like Januvia more than they are letting on; while Januvia at least isn't as efficacious as other drugs, it also lacks the side effects of hypoglycemia, weight gain, nausea, etc. On an upbeat note, Merck spoke about the strong progress the company has made in increasing access to Januvia and Janumet. We must say we have also been impressed that payors are stepping up as quickly as they seem to be; this is partly due to Merck's smart pricing strategy – no premium for Janumet. There are currently over 200 million lives reimbursed on the second and third tiers, representing about 90% of targeted lives; 165 million have access to Januvia (72% of targeted lives) and 140 million have access to Janumet (58% of targeted lives – and, we presume, climbing). Merck appears to have used managed care muscle in gaining coverage – unrestricted second tier formulary has happened faster than we had expected.

- **Bristol-Myers Squibb—Dapagliflozin follow-up, but still no real word:** Also at the Bear Stearns conference, CEO James Cornelius spoke on September 10 mostly about the patent expiration of the drug Plavix, the financial implications, and BMS's response. However, the Q&A drew much attention to BMS's diabetes franchise. Cornelius explained that dapagliflozin has just completed phase 2b studies and that the results "may" be presented at the ADA meeting in 2008. The company did relate that the phase 3 trials would include between 500-1,000 patients – certainly easier to enroll than many trials. Management added that it could be first-in-class since it has potential anti-obesity implications – many things would need to go right, in our view, for it to get this indication; and we imagine the studies would need to be extended from current plans.

- **Novo Nordisk—An update on US growth and liraglutide:** At the Bear Stearns conference on September 10, President Martin Soeters called attention to Novo Nordisk's increasing US presence and continued growth. Novo Nordisk has a higher percentage of market share in Europe and Japan than in North America, where it has approximately 43% of the insulin market, but that number is growing. The company once had only 400 US employees, and now that number has grown to 4,000 – last year alone, the company increased the size of its US insulin sales force by 700 people. China was highlighted as a geographic focus. While several of the company's patents will expire in 2013, management underscored that a number of newer insulins in phase 1 will hopefully come on board by the time the company's current portfolio goes generic. We are very interested to know what these insulins are – faster? cheaper? better? There is definitely something afoot on this front as this has now been highlighted several times in analyst meetings and conference calls.

On the liraglutide front, management still expects a launch following FDA approval in 2009, tantalizingly close to the expected LAR launch from the Lilly/Amylin team. Management said it will seek to target patients treated with orals who are poorly controlled, rather than patients who are on insulin – smart, since there are several million patients in the US alone not at glycemic target who remain on orals rather than moving to insulin. Specifically, Soeters said he expects that 80% of patients treated with liraglutide will come from oral therapy only. We don't know what the denominator is in hard numbers but would be very curious! It's been said that Novo Nordisk plans to apply for a very broad label for liraglutide – it will be interesting to see how the patient profile for the drug differs for that of Byetta.

- **BD—Mid-quarter update**: Chairman, President and CEO Ed Lugwig spoke broadly about BD's commitment to enhancing diabetes treatment during his talk September 11 at the Bear Stearns conference. Other remarks focused on reducing the spread of infection while advancing drug delivery. He said that BD is currently looking to find new ways, beyond insulin delivery, to enhance the lives of people living with diabetes. Although investors are interested in learning more about LAR needles and what this does to the pen needle franchise, there was no information on this front. We do believe that a recent Sanofi-funded insulin public service campaign should help BD – there have been two full-page ads in the *WSJ* recently. BD is unaffiliated with the campaign but should benefit.

- **Insulet—Tackling manufacturing constraints:** CEO Duane DeSisto spoke at the most excellent Thomas Weisel conference last week. He covered a broad range of topics and we appreciated his expertise on and candor about the market, broadly speaking. In speaking about the market's response to Insulet's OmniPod, he attributed a large part of the strong patient reviews to the simplicity of the product – we heartily agree and see this as both a patient and HCP advantage – as well as a payor advantage since pump delivery is so much more stable than even MDI (multiple daily injections).

  On the marketing front, the company now has 15 sales reps, up from five a year ago; a total of 30 are planned in 2008. Saturation of the market for pumps broadly has been a frequent investor question over the years and remains one today – DeSisto emphasized his view that current penetration into the primary care market was strongly hindered by onerous training procedures. We believe there are opportunities to expand into primary care where the doctors are insulin specialists - and we emphasize that more type 1s see primary care doctors than one might imagine, due to the growing endo (particularly pediatric endo) shortage.

  In terms of manufacturing, DeSisto made clear in his remarks that manufacturing constraints are the next big hurdle on which the company is focused; specifically, Insulet aims to have a fully loaded cost of production of $15 per pod by the end of 2008 at a volume of 200,000 pods per month. DeSisto outlined a savvy plan to achieve this goal, pointing to a shift in manufacturing of the front half of the chasis sub-assembly of the product from their facility in Bedford, MA, to a facility in China through their partnership with Flextronics. Unbelievably (or not), manufacturing of this component, which constitutes about 50% of labor costs for the device, costs $15/hour at the Bedford facility compared to $0.90/hour at the Chinese facility. Reports from manufacturing experts are that that early lots have been excellent – the same team working on this has built outstanding meters for J&J and Abbott, so this is indeed an impressive group. Insulet is currently in negotiations to have Flextronics responsible for building whole units, an endeavor that would cost Insulet $9 million in investment capital - this would be a real win if it could happen. As we understand it, this $9 million would duplicate the current start up and test models so that quality assurance designed for the current pods will be replicated. Excellent news for patients..

- **Medco-PolyMedica: Historic deal could forecast cuts to healthcare costs:** August 28th 2007 saw the publicizing of a definitive agreement wherein Medco would acquire PolyMedica in an all cash transaction valued at $53 per share or $1.5billion. The nations premier advanced pharmacy practices + leading provider of diabetes blood glucose testing supplies and related services = The nations premier provider of diabetes care services covering 3.8 million patients! PolyMedica brings 1 million diabetes patients to join Medco's 2.8 million patients. We believe that this win-win situation works to the advantage of both patients and industry. Medco already fills over 50,000 PolyMedica prescriptions weekly and PolyMedica provides Medicare Part B administration services and supplies to Medco patients. It is a huge advantage for diabetes patients to have these vital components of their therapy - testing supplies and drugs - under one umbrella since this should ultimately streamline the process from prescription to delivery. On Medco's side, they gain access to 1.0 million new patients who likely need lots of drugs, while Polymedia gains access to 2.8 million new patients who need strips. The transaction is expected to close later this year. PolyMedica CEO, Patrick Ryan, looks to Medco's clinical care solutions to aid his company perfect care to patients. This partnership, combined with a successful business history makes his case compelling. Medco CEO, David Snow, had similar comments on PolyMedica, prizing its strong business and experience in the field. This business partnership is certainly off to a good start.

- **BMS and Pfizer—A partnership to develop DGAT1 inhibitor class:** On August 27, BMS and Pfizer revealed a few more details about their partnership on a type 2 drug (now disclosed as a DGAT1 inhibitor) previously noted in April. In the agreement, Pfizer is taking the lion's share - 60% versus BMS's 40% - of the expenses and risk. It will control R&D and overall development until phase 3 (if it gets that far), at which point it will share costs. Pfizer will retain 60% of revenues and profits (or losses), and the companies will jointly conduct commercialization activities. The agreement applies not only to DGAT1 inhibitors developed by Pfizer, but also two DGAT1 inhibitors licensed to Pfizer from Bayer. In its press statement, Pfizer underscored that this collaborative agreement would pool the strengths and resources of both companies to expand their product portfolios.

  Relatively little information is available on Pfizer's DGAT1 inhibitor compounds, and the compounds remain in pre-clinical stages of research. The DGAT1 enzyme plays a critical role in the creation of fat storage in mammals. Compared to control mouse models, DGAT1-deficient mouse models have increased energy expenditure without a comparable increase in food intake, and have decreased levels of triglycerides. The DGAT1-deficient mice also have increased insulin sensitivity as well as leptin sensitivity. Given that obesity and diabetes are frequently comorbid conditions, the fact that DGAT1 inhibition could prevent both obesity and insulin resistance is potentially very exciting.

  We underscore that there are several reasons for caution with DGAT1 inhibition. Mice totally lacking DGAT1 (DGAT1 knockout mice) have several serious side effects, including skin dryness and back hair loss; and female DGAT1 knockout mice have problems in the development of the mammalian glands following pregnancy. These side effects are not seen with partial inhibition of DGAT1 in mice, but these data are concerning nonetheless. The DGAT1 enzyme is expressed in many different types of cells throughout the body, and it was initially thought that the benefits of DGAT1 were derived only from inhibition of the enzyme in adipose tissue. However, some more recent data from the laboratory of Dr. Robert V. Farese at UCSF suggest that specific inhibition of DGAT1 in the intestine may produce many benefits. This may be good news, because it may therefore be possible to get a positive effect through DGAT1 inhibition in the intestine with oral medication without exposing other tissues. This remains an area of active research.

- **AtheroGenetics—Disappointing results for AGI-1067 but moving to phase 3:** AtheroGenics had disappointing news recently on its lead compound, AGI-1067, an oral anti-diabetic that has anti-inflammatory and antioxidant properties, which is now in phase 3. In this post-Avandia-downfall world, a compound that offers positive diabetes and cardiovascular effects is potentially exciting; however, the success of AGI-1067 is certainly in question following recent data shown in Europe. The compound was previously in phase 3 for its ability to reduce major adverse cardiovascular events in a trial called ARISE (Aggressive Reduction of Inflammation Stops Events). The results were presented at the European Society of Cardiology in early September . In this trial, AGI-1067 failed to meet its target goal of reducing major adverse cardiovascular events, and although AGI-1067 produced improvements in glycemic control for the subsection of the population with pre-specified diabetes, the improvements were statistically significant but quite modest nonetheless – just 0.26% A1c reduction after 12 months. In spite of these underwhelming ARISE results, AGI-1067 is moving forward to a phase 3 diabetes trial called AGI-1067 as a Novel Anti-Diabetic Agent Evaluation Study (ANDES). The double-blind placebo-controlled study will take place at multiple sites in four regions – South Africa, Eastern Europe, India, and the United States. The 1,200 study participants will be randomized to receive 75, 150, or 300 mg of AGI-1067 or placebo. The study should conclude in late 2008, following a successful interim analysis in mid-2008.

- **GlucoLight snags Dr. Furnary for scientific advisory board:** Persuading a luminary like Dr. Furnary to be on the scientific board of a development-stage company is a real win – getting the focus of this man is likely difficult (we imagine his phone pretty much rings off the hook nonstop) but we also know he doesn't do anything halfway – so if he says he'll help, there's probably a good chance he can help in a meaningful way. Furnary's focus is blood glucose monitoring in the acute care environment – if you haven't heard him speak before, sign up for the next ADA / AACE / EASD, etc. It's really a wonderful experience because he is so passionate about changing a field. All that said, the competition in this tight glycemic control hospital-based field is certainly heating up – we'll be interested to follow what happens as we're very optimistic about the area. The next major meeting on this front is in Hawaii in February – this is definitely not one we'll miss. Those interested should go to the following link to read about "Glycemic Control and Metabolic Dysregulation in the Critically Ill and Injured" - see www.sccm.org/SCCM/Annual+Congress/Post-Congress+Event/. This is in Kauai February 6-8 – what is not to like? Dr. Douglas B. Coursin is the conference chair and Roche is sponsoring the event.

- **Amylin hosts 3rd Annual San Diego Research Symposium on Type 1 Diabetes:** This August 16 symposium was presented by Amylin Pharmaceuticals and the Profil Institute for Clinical Research, and was held at Amylin's headquarters. President and CEO Dan Bradbury gave a short welcome in which he briefly discussed Amylin's pipeline and specifically the company's dedication to treating patients with diabetes. He noted that Amylin has 27 ongoing exenatide trials and seven ongoing pramlintide trials - very impressive in our view, particularly as we understand there are also a number of interesting investigator-initiated trials ongoing - lots of intriguing data to follow, no doubt. Although this was not a venue where any new data were shared (disappointingly! but not surprisingly), Bradbury did emphasize the company's commitment to be a leader in new therapies for patients with type 1 diabetes in particular. This was terrific to hear since we feel many companies could be doing much more on the type 1 therapeutic side but aren't because of uncertain prospects with a relatively small market. Notably, in the EASD posters we are now reviewing, there appear to be some very interesting data comparing pramlintide vs. mealtime insulin as add-on to basal insulin in type 2 patients. You

might wonder about our Bradbury "quotable quote" above regarding John Wood's job description. John Wood was recently appointed to manage Amylin's partnership with Eli Lilly.

Later in the day, Emmanuel Baetge, VP and CSO of Novocell, discussed a possible method of generating beta cells using embryonic stem cells. Since 2005, when the technique for producing beta cells from embryonic stem cells was first established, Dr. Baetge's group has achieved a 280-fold improvement in beta-cell yield. Still, considerable technical hurdles remain, and islet transplantation is only in the very early stages. Establishing a renewable source of islet cells will be crucial in turning islet transplantation into a viable practice. Pamela Itkin-Ansari, Assistant Professor at UCSD, also discussed encapsulation of islet cells. Although studies have verified that islet cells can survive and be protected through this technique, the viability of encapsulation remains uncertain. It is unclear, for example, how big the capsules would need to be to provide enough insulin for an entire person (an audience member suggested that at best the capsule would need to be the size of a dollar bill), and whether a renewable source of islet cells can be established.

—by Kaku Armah, Mark Yarchoan, and Kelly Close

4. First National Diabetes Public Service Campaign: Edgy Messages

The first national diabetes public service campaign will be launched on September 13 to highlight the importance of A1c levels – an unprecedented effort that uses provocative, edgy messages to highlight the devastating complications of America's growing diabetes epidemic.

The ambitious campaign was created by the Ad Council, the country's leading producer of public service advertisements. Over the years, the Council has produced some of the country's most enduring slogans, such as "Friends Don't Let Friends Drive Drunk" and "A Mind Is A Terrible Thing To Waste." Its diabetes campaign, "Know Your A1c," will cover the media waterfront – television, radio, print, billboards, and Web ads – and its message is that A1c numbers can be warning signals for future complications, specifically heart disease and strokes.

The campaign eschews stuffy medical rhetoric; its goal is to shock.

In one TV ad, for example, a fisherman pushes away from the dock and says, "It's a great day for fishing."

"Yeah," says the dock hand. "Too bad your boat is going to sink at 11:05."

A voiceover then asks, wouldn't it be great if we were warned of life's risks? If you have diabetes, your A1c test does just that.

"We wanted to push awareness as far as we could," said Tom Boyer, executive director of the Diabetes Care Coalition (DCC), which is comprised of advocacy groups and companies to promote better care through this public service campaign. "We found in focus groups that patients responded to dramatic messages" – heart attacks and strokes struck a much stronger chord than eye or kidney damage – "so we didn't want to coat it in any way. We wanted them to understand explicitly what they were facing."

Health professionals have understood the importance of A1c levels for years. The test measures average blood glucose over the past three months, giving a good gauge of glycemic control. However, many patients remain unaware, particularly in minority communities. Impressively, the public service campaign has been crafted in Spanish as well – but more than just translating English, it will feature specific messages that should resonate with Hispanics. The same is true for other demographic groups, including African Americans, women, and the elderly. (The Web site for the campaign is www.diabetesA1c.org.)

The A1c campaign culminates a five-year effort by the DCC, which is made up of traditional rivals, both profit and non-profit, who came together in an unprecedented collaboration. The country's two leading

diabetes advocacy organizations – the American Diabetes Association (ADA) and the Juvenile Diabetes Research Foundation (JDRF) – have not always worked together in the past, but they are the leading supporters behind the campaign.

Corporate sponsors are also behind it: Abbott Diabetes Care Inc., Bayer HealthCare LLC, LifeScan Inc., Novartis Pharmaceuticals Corp., Novo Nordisk Inc., Roche Diagnostics Corp., and sanofi-aventis U.S. LLC. The campaign is strictly educational. It does not endorse any products, and the corporate supporters are never shown.

Another contributor to the campaign is the National Council of La Raza, the largest Hispanic civil rights organization in the U.S., with a network of nearly 300 affiliated community-based organizations that reach millions of Hispanics each year in 41 states, Puerto Rico, and the District of Columbia. The American Association of Diabetes Educators (AADE) participated as well – it's critical to get educators involved, and its support of this campaign is testament to President Donna Rice's leadership.

The A1c campaign is expected to last three years, and we expect it will raise awareness of diabetes significantly. While the effort is part of the direct-to-consumer (DTC) advertising trend in health care, it poses no threat to clinicians – in fact, the campaign urges patients to see their health care providers and to ask about their A1c and what their goal should be. Because the A1c test remains the gold standard of care, its focus for the campaign makes sense. We do point out, however, that there is considerable debate about what the target A1c should be: the ADA, for example, says 7 percent or lower, while the American Association of Clinical Endocrinologists (AACE) says 6.5 percent or lower.

The campaign is using 7 percent, because, according to Boyer, that's the federal government's recommendation.

In one new television commercial, two parents are riding in the front seat of a car, with their child in the back seat playing a game but not wearing a seat belt. An ambulance drives up, and a medic says to her: your A1c is over 7%.

The theme is clear and the goal is laudable – to make diabetes patients realize that they lack clear physical warning signs for an impending physical calamity. So, test your A1c. Nevertheless, it's certainly possible that such a broad campaign, which suggests death, however amusingly, will offend some patients. Some may fear that the campaign could confirm the false stereotype that people with diabetes are already half-way to their grave.

But the various messages make clear that patients can reduce the risk of bad outcomes by lowering their A1c. Moreover, Boyer said that the pilot campaign, launched in January of 2005 in Tampa and Atlanta, demonstrated its effectiveness. "We learned we could do this and we could have a demonstrable impact in a short period of time," Boyer said. Now the national campaign offers much greater opportunities. "We'll be able to move the needle" for better care.

We heartily concur.

—by James S. Hirsch and Kelly Close

5. Literature Review: Avandia— At Sea, With No Port in Sight

Dr. Steven Nissen and colleagues published a meta-analysis in the September 11, 2007, issue of JAMA *indicating that pioglitazone (Actos, Takeda) has a favorable cardiovascular risk profile – a clearly meaningful advantage over rosiglitazone (Avandia, GlaxoSmithKline). In the study, pioglitazone significantly reduced the risk of stroke, myocardial infarction, and overall mortality. Accompanying this article is another meta-analysis by Dr. Singh and colleagues that shows the unfavorable long-term cardiovascular risks of rosiglitazone (Avandia, GlaxoSmithKline). The study found that the risk of*

myocardial infarction was increased 43% with rosiglitazone. The difference between rosiglitazone and pioglitazone in this regard is likely due to their different lipid profiles (rosiglitazone increases LDL-cholesterol to a greater extent than pioglitazone, and raises triglycerides while pioglitazone lowers them). Overall, these two meta-analyses, even given some stated limitations, are likely to catapult Actos' sales at the expense of Avandia's. We also expect a favorable impact on insulin and to a lesser extent incretins, especially Januvia, which is perceived as an easy (if not particularly effective) switch. Two editorials accompany these pieces; one ("CVD Risk and the TZDs – Déjà vu All Over Again?") proposes changes to the US drug safety system, which, if accepted, would increase the cost of drug development quite significantly, particularly for "me-too" drugs.

- **Dr. Steven Nissen and his colleague, Kathy Wolski, MPH, have an impressive history of calling attention to peroxisome proliferator-activated receptors (PPARs) drugs on adverse cardiovascular events.** It was their October 2005 *JAMA* article that led to the discontinuation of muraglitazar (Pargluva, Bristol-Myers Squibb and Merck) following a favorable panel review by the FDA. Less than two years later, it was their May 21, 2007 *NEJM* article on the cardiovascular risks of rosiglitazone (Avandia, GlaxoSmithKline) that prompted a meeting of an Advisory Committee of the FDA and a Congressional hearing about whether the drug should stay on the market. Avandia market share has plummeted significantly since the paper was published, from well over 10% to under 4%.
- **Since the time of Dr. Nissen's meta-analysis of rosiglitazone showing an increased risk of cardiovascular death associated with the drug, a question of great debate is whether this was a class effect** (and whether the study brought to light a real risk in the first place). If the increased risk of cardiovascular death was a class effect, it would seem to suggest that pioglitazone (Actos, Takeda) should share the same risk. Actos and Avandia are the only two approved thiazolidinediones (TZDs), and their effects on reducing insulin resistance are very similar. One key difference however, is that Actos has a superior lipid profile: Avandia raises LDL-cholesterol to a greater degree than Actos, and also raises triglycerides whereas Actos lowers triglycerides. The fact that the difference hadn't been marketed more strongly has been extremely surprising, even given that Takeda has never been viewed as the smartest marketing organization.
- **So with this history of scrutinizing PPARs, what do Dr. Nissen and his colleagues have to say about pioglitazone's effect on cardiovascular risk?** In their meta-analysis of 19 studies, Dr. Nissen and colleagues conclude that pioglitazone has an overall *favorable* effect on cardiovascular risk, independent of the reduction in cardiovascular risk associated with improved glucose control. In the studies reviewed, which included 16,390 patients from diverse populations, patients treated with pioglitazone had a significantly lower incidence of stroke and myocardial infarction (heart attack). Like rosiglitazone, pioglitazone causes edema (fluid retention/swelling), and so it was not surprising to find in this study that pioglitazone was associated with a higher incidence of serious heart failure overall. However, the authors found that despite causing a higher incidence of serious heart failure, pioglitazone was not associated with increased mortality – in fact, pioglitazone was associated with a significantly lower incidence of death, suggesting an overall positive cardiovascular effect. Thus, in our view, pioglitazone's reduction in irreversible ischemic events outweighs its increase in serious heart failure.
- **An accompanying meta-analysis published in the September 11 *JAMA* by Dr. Singh and colleagues examines the effect of rosiglitazone on long-term risk of cardiovascular events.** In total, four studies were included in the meta-analysis (14,291 patients), and each study was randomized, placebo-controlled, and at least one year in duration. Unlike pioglitazone, which may lower incidence of myocardial infarction, rosiglitazone was found to increase risk of myocardial infarction by 43% and double the risk of heart failure. However,

somewhat mysteriously, overall cardiovascular mortality was not increased by rosiglitazone. While the authors do not provide an explanation for why cardiovascular mortality is not significantly affected by rosiglitazone, they do suggest that the FDA labeling of Avandia is "outdated" and that the newest data suggest "a reversal of the benefit-to-harm balance… present at the time of approval." In light of this data, the authors go on to say that "regulatory agencies ought to reevaluate whether rosiglitazone should be allowed to remain on the market."

- **Also in the September 11 *JAMA*, an editorial by Dr. Solomon and Dr. Winkelmayer entitled "Cardiovascular Risk and the Thiazolidinediones: De´ jà Vu All Over Again?" reviews the history of the TZDs and uses this record to propose changes to improve the US drug safety system.** The authors advocate quicker and clearer regulatory action, such as black box labeling, in response to initial safety concerns, and they recommend requirements for phase 4 (post-marketing) studies. Additionally, the authors recommend replacing surrogate markers with true clinical outcomes, and more consistent requirements of drug safety. Thus the authors argue that any drug that would not be approved today (and they would argue that rosiglitazone falls into this category) should not be allowed to remain on the market, regardless of the inconvenience of drug removal for all parties involved. Finally, the authors recommend that the FDA derive a concrete method for weighing the benefits and harms of a drug. We feel that this last recommendation in particular is unfeasible – there is no mathematical formula that can possibly determine whether a drug should be approved, because risks and benefits are themselves extraordinarily difficult to assess and must be evaluated on a case-by-case basis.
- **The findings presented by Drs. Nissen and Singh that rosiglitazone and pioglitazone do not have equivalent cardiovascular risk patterns may have considerable implications on drug sales.** Based on the available data, pioglitazone has a favorable cardiovascular risk profile and rosiglitazone has an unfavorable cardiovascular risk profile. Given that all other aspects of the drugs are essentially equivalent, this suggests a potentially significant advantage for pioglitazone over rosiglitazone, which should eventually be reflected in sales. Historically, we have found it mysterious that rosiglitazone and pioglitazone had roughly equivalent sales early on, even though pioglitazone had a superior lipid profile. However, the potential difference between the drugs with respect to myocardial infarction, highlighted by the Nissen and Singh meta-analyses, is much more important and will have a drastic effect on their respective sales. We expect to see many patients switching from Avandia to Actos in the coming weeks and months. Overall, this should be very positive for Takeda, unlike in mid-May when this controversy first arose, when Actos suffered a great deal due to perceived "class effect."
- **Dr. Nissen's meta analysis may propel Actos sales beyond patients switching from Avandia to Actos.** From the time of Dr. Nissen's meta-analysis of rosiglitazone, there had been a general perception that the entire TZD class of drugs shared cardiovascular risks. Thus, while the Avandia fiasco primarily reduced Avandia sales, it also cast a dark shadow on Actos. Dr. Nissen's new meta-analysis of pioglitazone to a certain extent lifts that shadow.

—by Mark Yarchoan and Kelly Close

6. Literature Review: Nice Review, Pity About the Politics

In the September issue of Diabetologia*, Drs. Holleman and Gale argue that although many of the initial advances in insulin formulations dramatically improved clinical outcomes, human insulin and human insulin analogues have had relatively few clear clinical benefits for type 2 patients. Hypoglycemia is reduced in patients who are treated with short-acting insulin analogues, but these therapies, according*

to the authors, do not improve A1c beyond standard human insulin. Since most type 2 patients do not experience significant hypoglycemia (due to insulin resistance), the authors contend that in these patients, current evidence does not support the use of short-acting insulin analogues.

- **The article is valuable, in our view, for its insightful (and controversial) rendition of the history of insulin.** As the piece notes, Eli Lilly released the first recombinant human insulin in 1983; however, the authors argue that human insulin provided no clear benefit above the standard pork insulin apart from marketing advantages[1]. The authors say this is in contrast to earlier advancements in insulin production. Highly purified, recrystallized insulin significantly reduced allergic reactions to insulin; methods to slow insulin delivery through the introduction of protamine (NPH insulin) or the formulation of zinc salts (lente insulin) permitted once-daily dosing, a major convenience. Despite lacking clear benefits[2], the authors say that Novo Nordisk attempted to drive doctors to switch their patients to human insulin by withdrawing pork insulin from the market.

- **The authors do explain that genetically modified human insulins were developed in response to several clinical problems associated with the use of human insulin.** Human insulin is absorbed slowly and remains in the plasma for extended periods of time, leading serum glucose to rise too high after meals and to fall too low between them. Formulations with faster absorption (intermediate-acting insulins) still predisposed patients to hypoglycemia, particularly at night, but those insulins are cleared from the plasma before the next morning, producing surges in plasma glucose. In addition, absorption of human insulin is often erratic, leading to significant fluctuations in insulin activity.

- **To follow, the authors explain that rapidly acting insulin analogues decrease the risk of hypoglycemia, but do not clearly improve A1c values in type 2 patients.** The implication is that if it doesn't improve A1c, it's not really worthwhile, a view we would strongly oppose. Clearly type 1 patients experience more hypoglycemia than type 2 patients, but many type 2 patients do experience it – particularly the elderly (SFUs cause hypos and have been criticized for this for some time). Insulin lispro (Humalog by Eli Lilly) and insulin aspart (Novolog by Novo Nordisk) were the first rapid-acting insulin analogues to reach the US in 1996 and 1998 respectively. Both analogues were developed to reduce insulin self-aggregation and provide better postprandial glucose control without increasing the risk of hypoglycemia. Humalog and Novolog were marketed as more convenient formulations, which could be injected closer before a meal than could regular insulin. For the most part, blinded comparisons to human insulin were not performed on the grounds that differences in injection protocols would prevent blinding. From our view, we feel confident that better postprandial glucose control in type 2 patients on rapid-acting analogues would be evident and that less hypoglycemia would also result; however, the article vaguely states that patients were not able to sense these benefits. While A1c levels were identical in the two groups, we believe the group on analogues may well have experienced more stability and less hypoglycemia – and although the group may have seen the same A1c, it may have been a healthier A1c as the standard deviation of blood glucose levels leading to the A1c may have been lower (data not given, unfortunately). The fact that the piece focuses almost exclusively on A1c levels highlights to us that globally, the field remains too A1c-centric; i.e., insufficient

[1] Editor's note - I was diagnosed with type 1 in 1986, and doctors certainly told me at the time how lucky I was to avoid animal insulin, though I wasn't given any quantitative information on why the new insulin was better. - KC

[2] We note the average type 1 patient who has taken the "non-analogue" insulins would likely say that the analogue insulins are far more stable and produce less hypoglycemia; the authors would counter that type 2 patients experience less hypoglycemia. The authors basically concede that for some type 1s, analogues are significantly better – we don't know any type 1s who would choose an older insulin over an analogue, though the authors imply there is little benefit to analogues for anyone.

attention is paid to the quality of the A1c (a higher-quality A1c, in our view, is one with lower standard deviation).

- **The article also states that in patients with type 2 diabetes, long-acting insulin analogues have no clear effect on A1c above standard human insulin** and show "only a modest decrease" in the risk of hypoglycemia, with the implication that this is unimportant. From our view, the market has clearly shown that a more stable insulin, as found in a long-acting analogue, is valued, since this market exceeded $2.0 billion in 2006 – the article implies this is due almost purely to marketing. It does give a history of the product, noting that the first successful long-acting insulin analogue was introduced by what is now Sanofi-Aventis (Lantus or insulin glargine) in the US in 2000. Lantus was followed in the US by insulin detemir or Levemir from Novo Nordisk in 2004. Both analogues were developed to decrease preprandial glucose levels and to provide basal insulin coverage. Double-blind studies were not performed on these analogues; however, open-label "treat-to-target" studies on insulin glargine found a 15-20% decrease in nocturnal hypoglycemia in patients with type 2 diabetes. Since nocturnal hypoglycemia is "only" experienced by 30% of patients with type 2 diabetes (well over 4 million patients in the US alone the last time we checked), this was characterized as a "relatively modest" benefit. The article also noted that Levemir appears to produce less weight gain than human insulin on initiation of therapy (approximately 1 to 1.5 kg) and has a similar effect on the risk of nocturnal hypoglycemia.

- **Current German guidelines suggest that rapid-acting insulin analogues are appropriate in just a small population of intensively managed patients** – this seems absurd to us, because we assume most clinicians believe that the more patients who can manage their diabetes more intensively, the better (the article seems to suggest intensive management should be seen in only a small percentage of patients). Safety is the main issue, and analogues clearly provide more safety because of less hypoglycemia. The fact that A1c's may not change significantly, in our view, might just suggest there is less variability, which may also be a benefit though this has not been proven. If anything, in our view, this article raises the importance of doing studies that more definitively to show the significance of glycemic variability. The authors clearly think insulin analogues, which claim roughly 40% of the insulin market, should be used by far fewer people with diabetes. We note that human insulin is barely growing, while analogues are experiencing extremely strong, 20%-plus growth – clearly the market believes in the value, though the article states that Lantus has strong support from many patients and doctors, despite the absence of a clear clinical benefit! In part, the authors say this support may derive from increased enthusiasm and motivation associated with the change in insulin therapy, as well as increased attention to other aspects of patient care during the transition. Well-designed, blinded studies are the only way to resolve the extent to which patient-perceived improvements in diabetes management are the result of improvements in insulin function, and we would certainly advocate more of these in the future.

- **The authors conclude that although evidenced-based medicine has limitations, it should have a central role in guiding clinical decisions**, though it should not strictly dictate the course of action. Clinical trials can overlook important benefits in subpopulations, and open-label studies can be biased by familiarity with the use of older therapies. If anything, in our view, this statement should prompt greater use, not less use, of analogues.

- **The article concedes that preliminary evidence does appear to support insulin analogues in intensively managed patients with diabetes.** If dose titrations are performed carefully, intensively managed patients can experience tighter glycemic control and a reduced risk of hypoglycemia – of course in our view, every patient should experience tighter

control and less hypoglycemia! However the authors state that patients with poor glucose control are unlikely to derive a benefit from insulin analogue therapy, since, in this population, high overnight glucose levels are the primary contributing factor to total A1c – and they note that this population comprises a large fraction of patients with type 2 diabetes. We would counter that if there is such a big group of patients with poor control, maybe absence of good, easy, well-covered therapies is the problem – this article, in our view, advocates insulin-dependent patients moving backwards rather than forwards.

- **The conclusion to the piece was wrong, in our view.** The authors say in their conclusion that if healthcare purchasers only reimbursed for high-cost medications with a demonstrated clinical benefit, this may reduce drug costs and improve the quality of clinical trials. Although the IQWiG did reduce the immediate costs of analogues in Germany, we expect that if the same happened everywhere, fewer funds would go towards R&D. This would be bad for patients for obvious reasons, bad for healthcare providers because less investment likely means fewer alternatives, and bad for payers because this will likely result in higher costs for patients with complications – the most expensive patients to cover by far.

—by Michael Dougan, Mark Yarchoan and Kelly Close

7. Online Technology Holds Promise to Connect Patient and Provider and to Empower Patients to Become Healthier

Flying solo is difficult with diabetes.

Research studies have shown – and common sense would confirm – that patients with diabetes are more motivated when they are encouraged by a doctor, nurse, or educator; but our health care system doesn't adequately pay for sustained professional guidance or encouragement.

Dr. Neal Kaufman, CEO of the Diabetes Prevention Source, believes that technology can help solve this problem by allowing patients to interact with health care providers in a useful, seamless – and economically viable – fashion. In his scenario, the bulk of the communication is done online – which is not quite as powerful as a real-life smile or an empathetic hug – but patients can now receive timely information and support at a moment's notice and connect with kindred spirits from all over the world. Even a virtual shoulder to cry on is better than none at all.

Dr. Kaufman, who spent the bulk of his career in academic general pediatrics at Cedars-Sinai Medical Center and UCLA School of Medicine, says a diabetes nurse educator or dietician is like a coach whose job is to help patients adopt and sustain healthy lifestyles. "They are there to help a person over time implement healthy behaviors," he said, "and then, most importantly, make it into a habit."

The problem is that an individual educator or dietician can only see so many patients. Online technology, however, "has the capacity to mimic, though not duplicate, that human interaction," Dr. Kaufman said. That would allow a single "coach" to serve far more patients, which in turn would save money and eventually generate revenue so that these online visits would be more feasible financially.

Dr. Kaufman has enough faith in this idea that in 2004 he left his 26-year career in pediatrics to found the Diabetes Prevention Source (DPS). Its co-founder is even better known than he: Dr. Francine Kaufman, Neal's wife, is the past president of the American Diabetes Association and director of the Comprehensive Childhood Diabetes Center at Childrens Hospital Los Angeles.

Neal Kaufman describes the company's online products as a "technology platform married to a research-proven curriculum or protocol to create an intervention." The University of Pittsburgh's Diabetes Institute worked with DPS to develop and evaluate a product called "VLM," or "Virtual Lifestyle Manager."

Starting in November, it enrolled 50 subjects supported by 0.4FTE nurses, and after one face-to-face meeting, all other interaction was done online. The patients use the VLM which has streaming audio,

interactive workbooks, quizzes, and journals, and communicate with their nurse – what they ate, how much they exercised, etc., -- through the program. The nurses, in turn, would evaluate every week the patient's understanding and performance and send back an email.

Does a "Virtual Lifestyle Manager" actually get people to change their lifestyles? The results of this study will not be presented until next year, but Dr. Linda Siminerio, the director of the Pittsburgh Diabetes Institute, said, "So far, we have very encouraging results. It's a good support tool, though there still needs to be some human contact."

Dr. Kaufman said all he and the Diabetes Institute are doing is applying to the Internet the same principles that worked in the Diabetes Prevention Program, which ended in 2002. In the DPP, which had 3,200 subjects, regular face-to-face meetings with providers (once a week for 16 weeks and periodically thereafter) decreased the progression from pre-diabetes to diabetes by 58 percent.

Direct intervention helps patients maintain healthy lifestyles; so, according to Dr. Kaufman, the biggest benefit of the Internet is that the intervention is much less costly. He believes that the VLM will soon have a provider-to-patient ratio of 1:200 or 1:300 making his product "affordable and scalable." DPS's other product—its Physical Activity Prescription - is an on-line coaching intervention that helps sedentary adults become more active and needs less than 90 minutes of human coaching over 6 months.
Technology is not usually associated with the "softer" side of diabetes care, such as motivation and behavior. It is usually used for such things as improving how insulin is delivered or how blood sugars are measured. But Dr. Kaufman recognized that unhealthy lifestyles are overwhelming conventional therapies – a topic deftly explored in his wife's book, *Diabesity* – and that appropriate intenet intervention can work.

"If you look at the basic physiology of humans, we are addicted to sugar, salt, fat, and inactivity," Neal Kaufman said. "Those four addictions were actually quite essential to the preservation of the human species when we had famine all the time and when we ran around trying to capture our food or to gather it."

But now those addictions have led to the emergence of lifestyle-driven maladies – type 2 diabetes, obesity, hypertension – that individuals are capable of combating. That is very different than the traditional view of disease, in which the individual has no control. "Most individual behaviors are unimportant in a person's outcome, but the sum of all those behaviors is critical," he said. "That is a very different paradigm, because the patient really is in control of their micro-behaviors. So the question becomes, 'How do you help individuals take adopt and sustain healthy habits?."

He recognizes that technology will not solve all our problems, that it's only one piece of the puzzle. But what's exciting about technology is that it's only going to get better – cell phones that can test blood sugars, deliver insulin, measure physical activity, provide counseling for example, or even an artificial pancreas.

Or if Dr. Kaufman has his way, a nurse who will text-message a far-away patient with some quick reminder, some whimsical nudge, helping him to know that he is not flying solo.

—by James S. Hirsch and Kelly Close

8. In The News: A Fresh Look at Bariatric Surgery

This month, two landmark studies published in the New England Journal of Medicine *convincingly demonstrate for the first time that bariatric surgery (used to treat morbid obesity) reduces diabetes and long-term mortality in severely obese patients. The organization formerly known as the "American Society for Bariatric Surgery" (ASBS) responded by changing its name to the American Society for Metabolic & Bariatric Surgery (ASMBS) and will now focus on bariatric surgery as a treatment that goes beyond weight loss. It is likely that scientists, health care professionals, and patients will take a fresh look at bariatric surgery.*

- **People are taking a fresh look at bariatric surgery (used to treat morbid obesity) in light of two landmark studies published in the *NEJM* on August 23.** These studies provide for the first time strong evidence that bariatric surgery reduces long-term mortality in severely obese patients. In one study called the Swedish Obese Subjects (SOS), Sjostrom and colleagues show that bariatric surgery reduces overall mortality by 29% in ten years starting at surgery. And a retrospective cohort study by Adams and colleagues found bariatric surgery reduces mortality by 40% and death from diabetes by 92% in 7 years starting at surgery. Even more impressive, despite the high risk of bariatric surgery, deaths in the first year were essentially the same in both groups. In both studies, patients had an average BMI above 40.
- **An accompanying editorial by Dr. George A. Bray argues that the criteria for bariatric surgery may "need to be reexamined"** in light of the latest evidence. He points out that in the years since bariatric surgery was performed in the Adams and Sjostrom studies, laparoscopic techniques have largely replaced open operative techniques, further reducing mortality associated with the procedure. Given that bariatric surgery reduces the risk of diabetes and other diseases and improves life span, Dr. Bray contends that it may be time to lower the BMI guidelines for bariatric surgery.
- **In the 1980s, the National Institutes of Health (NIH) produced guidelines about bariatric surgery** indicating that the treatment should only be considered for patients with a BMI of more than 40, or more than 35 for patients with coexisting illnesses like diabetes. Additionally, the guidelines state that the treatment should only be considered if all other forms of treatment have failed. See the NIH guidelines at win.niddk.nih.gov/publications/gastric.htm. Due to the tremendous risks associated with the intensive surgery, it is considered the most drastic measure and an absolute last resort. Despite these risks, the *New York Times* reported in its coverage of the *NEJM* articles that nearly 180,000 patients underwent gastric-bypass operations in the US last year, at an average cost of approximately $25,000. This is very high, but then again drugs can easily exceed $3,000/year for patients with more advanced type 2 diabetes – so the ROI on bariatric surgery might ultimately actually prove to be be quite good. We believe that the number of patients undergoing this procedure will increase in light of the latest data, as bariatric surgery is framed as a health intervention rather than a cosmetic surgery.
- **The two *NEJM* studies coincided with an interesting announcement from the organization formerly known as the American Society for Bariatric Surgery (ASBS) that it is adding "Metabolic" to its name.** This is the first time the 3,000-member organization has changed its name since its inception 25 years ago. The organization will now be called the American Society for Metabolic & Bariatric Surgery (ASMBS). The organization's press release states that "mounting evidence suggests [that bariatric surgery]… may be among the most effective treatments for metabolic diseases and conditions including type 2 diabetes." The organization says this name reflects the organization's new focus on bariatric surgery as a treatment that goes beyond weight loss. We find the name change very interesting – it would seem to help surgeons who would like to target bariatric surgery at those with metabolic disease, not just those who are morbidly obese – traditionally the target for bariatric surgery.
- **Bariatric surgery has never been considered a treatment for type 2 diabetes, but this could change with time in light of the most recent data.** We could start to see an increase in the number of bariatric surgery posters at next year's major diabetes conferences (ADA, AADE, etc.) Now that studies have provided strong evidence that bariatric surgery can reduce diabetes and ASMBS is expanding its focus to curing metabolic diseases such as type 2 diabetes, it is likely that scientists, health care professionals, and patients will take a fresh look at this procedure.

--by Mark Yarchoan and Kelly Close

9. In the News II: A dLife Update

Quick update on dLife – it's all about the web. dLife continues with its video show but the real power in its model is its ability to impact patients via the web. dLife hit the top three online positions according to comscore in diabetes, right behind WebMD and MSN. Impressively, dLife has the most repeat visitors and the most page views. Currently, the site touts more than 400,000 unique visits, and its plan is to reach 600,000 unique visitors by early 2008 and 700,000 opt-in members. dLife certainly has a great chance to dominate the web – currently it has over 10,000 pages, 5,000 recipes, and 200 video streams, not to mention expert Q&A, a support forum, and tips for diabetes savings. While dLife is now a powerhouse on the web, its TV presence has grown as well. Whereas in 2005 it had an average of 125,000 viewers per show, it now has an average of 460,000 viewers. It's estimated in the aggregate dLife's audience includes about 50% of diagnosed diabetes households in the US – incredible!

We are especially looking forward to the September 16 dLife program (repeated on December 30) about a ten year old pilot program in Asheville, N.C. that utilizes pharmacists to reach out to patients with diabetes early and often, and provides free medication for patients. We first discussed this program in the January 2007 issue of DCU. The results of the program were improved patient outcomes and reduced health care costs for their employer (the city of Asheville). This pilot program confirms that sustained interventions have significant benefits for patients and may even save money in the long run. We're greatly awaiting an update on the success of this program from dLife.

Diabetes patients and their families should also tune in to the September 23 dLife show, which will answer frequently asked questions about health insurance. We're continually impressed with how dLife remains on the cutting edge and keeps patients up to date. As demonstrated by the upcoming September 23 show, dLife focuses on the most important things for diabetes patients, helping them to better manage their disease and live a freer lifestyle. Check out dLife on the web at www.dLife.com or Sunday nights on CNBC (among other various cable channels).

—by Kelly Close

10. Conference Preview: Cleveland Clinic Obesity Summit

September 27-29 • Cleveland, OH • www.clevelandclinicmeded.com/obesity07

The Cleveland Clinic's second annual obesity summit will be held on September 27-29 this year. This relatively cozy CME meeting on trends and treatments for obesity is an excellent opportunity to meet clinicians involved in the care of obese patients. It will begin with an industry-sponsored day of programs followed by one and a half days of practice-focused clinical programs. The conference is largely single track so it should be easy to attend all the talks; below we offer our recommendations for the ones we're looking most forward to.

Thursday, September 27 – Industry Program

Thursday will begin with an introductory session at 8:00-10:10 a.m. on the "*State of the Disease State*." Dr. Lee Kaplan, Director of the Massachusetts General Hospital Weight Center, will discuss "Lessons learned from the bench: Molecular targets for obesity therapy," which may lend some insights into future drugs for obesity. Afterwards, Dr. Antonio Tataranni, Dean Geraci, and Dr. Donna Ryan will speak, respectively, on challenges in drug development, device development, and real world implementation. Dr. Ngozi Erondu from Merck will conclude the session with a very helpful talk on "New guidance: Implications for clinical trials in the FDA approval process." We would be fascinated to hear about the status of Merck's phase 3 CB1 receptor antagonist, taranabant, though we're not sure if Dr. Erondu will

discuss the specifics of how the FDA panel's decision on rimonabant has affected Merck's program. From 10:45 a.m.-noon, a group of industry representatives will host a round-table discussion and Q&A regarding "*Entrepreneurs' Experience in Obesity: Perspectives from the Trenches*." We expect that the focus here will be mostly on bariatric devices and equipment rather than drugs.

The afternoon will begin with an important session at 1:15-3:45 p.m. on "*Trends in Obesity Technology: What's Hot and What's Not*." Dr. Kaplan will give an overview of the current trends, followed by Dr. Richard Atkinson of the Obetech Obesity Research Center on "New drugs in development" – an important talk for anyone interested in the medical treatment of obesity. We're curious to see what Dr. Atkinson thinks the most promising treatments in the pipeline are. He will be followed by bariatric surgeon Dr. Philip Schauer, speaking on new devices/procedures, and Cleveland Clinic Health and Wellness program director Dr. Michael O'Donnell, speaking on workplace strategies. The day will conclude with a session and panel discussion at 4:10-6:00 p.m. on "*Reimbursement Issues*," which will feature talks from various speakers representing the perspectives of the employer, insurance industry, patient advocate, and drug/device manufacturing industry.

Friday, September 28 – Clinical Program

Dr. David Kessler, former FDA Commissioner from 1990-1997, will give the keynote address on Friday morning at 7:40-8:30 a.m. Dr. Kessler was responsible for the FDA's move to require food labels on the products we take for granted today in the supermarket. We're very much looking forward to his talk on "*US Government Obesity Initiatives*."

Following the keynote address, Dr. Steven Nissen will moderate an 8:30-10:20 a.m. session on "*Biologic influences on Obesity*," which will cover the roles of biology, metabolic influences, and viral mechanisms on obesity. The morning will conclude with a 10:40 a.m.-12:15 p.m. session on "*Metabolic Syndrome and Obesity*," which will include three talks on the links between insulin resistance and the metabolic syndrome, obesity and dyslipidemia, and obesity and hypertension.

After lunch, from 1:30-3:20 p.m. there will be a session on "*Therapeutic Management: Lifestyle, Nutrition, Behavioral Approaches*," with talks on lifestyle challenges for exercise, diets and nutrition, and behavioral strategies for weight loss. Following this, there will be three consecutive workshop sessions at 3:50 p.m., 4:25 p.m., and 5:00 p.m. We're looking forward in particular to Drs. Donna Ryan and Sangeeta Kashyap's workshop on "Weight loss challenge: Patients with diabetes" and Drs. Philip Schauer, Gary Foster, and Robert Kushner's session on "Management of medical-surgical patients." Other options include workshops on commercial diet websites and motivational strategies for weight loss.

Saturday, September 29 – Clinical Program

The last half-day of the meeting will be an action-packed review of pharmaceutical and surgical options for obesity treatment. The morning will begin with an 8:00-10:00 a.m. session on "*Therapeutic Management: Pharmaceuticals*," which opens with a talk on the FDA approval process and drug pipeline. Afterwards, obesity expert Dr. Louis Aronne from Cornell will talk about "Incorporating pharmaceutical therapies into clinical patient management strategies" – we're very interested in what he has to say about the best options for weight loss, and particularly his views on the potential roles of Byetta, liraglutide, Symlin, and rimonabant in weight management. Dr. Raj Padwal from University of Alberta Hospital will conclude the session with a discussion of "Relative efficacy of new and existing drugs."

At 10:30-11:15 a.m., Drs. Philip Schauer and Bipand Chand of Cleveland Clinic will perform live surgery demonstrations of gastric bypass surgery and lap band surgery. These are not for the faint of heart, but certainly worth watching for those interested in seeing the guts of the procedures. They will be followed by a series of talks on the management of patients after bariatric surgery. At 12:15-12:35 p.m., Dr. Francesco Rubino from the European Institute of Telesurgery will conclude with a discussion of the mechanisms of

action behind bariatric surgery; we'll be interested to see the extent to which he discusses the role of the changes in satiety hormones such as GLP-1 and ghrelin that occur after surgery. *—by Jenny J. Jin*

11. Random Thoughts

Our art tip for the month is Richard Misrach at the Chicago Art Institute – we're going to the opening this evening, changing planes in the windy city before heading toward Amsterdam. Our favorite kind of efficiency, when business travel enables art recess… www.artic.edu/aic/exhibitions/exhibition/beach.