DIABETES CLOSE UP

**Diabetes Close Up**
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***DCU on Pre-Diabetes~ Early AADE Download***

**T h e S h o r t e r V e r s i o n**

*From the Editor:*

*Happy summer! We're in the thick of it in Washington DC … 'It's getting hot in herre …'*

*Yes, we're at AADE – the conference is most excellent! My most favorite thing is to linger in the convention center and talk to CDE's – talk about smart and savvy and how lucky we are to have them helping focus diabetes education and treatments. We continue to be (dumb)struck by how poorly reimbursed CDEs are (and are diabetes HCP in general) – the ROI on diabetes education must be a trillion! As it always seems to at this meeting in particular, the challenges of diabetes loom ever larger and the only way we have a fighting chance in our view is to attract more CDEs. More on that to follow! So AADE – well, a LOT of exciting launches are going on here! We'll have a full report in September (in case you are here – our calendar is posted on our site), but for now, we can say Insulet's launch of its Omnipod is reaping well-deserved attention from the CDEs and we suspect what it'll do for market expansion overall will be sublime! Elsewhere in device-land, Roche has a number of launches, including the Aviva meter - they fixed everything (!!) and made yet another quite-something "I am..," commercial, the first one ever for Aviva rather than Compact. No news on Bergdorf except that the FDA has come and gone. I asked some reps if the agency was still smiling when it left, but we got zero input on that. We assume the best. In other news, Abbott has a very cool new strip and Precision Xtra - it's now down to five seconds from the seven-second strip I had been using with Flash and the new Xtra is really very sweet! A brilliant R&D exec just shook his head when I exclaimed over the two-second time advantage, and I showed him the quick math that this is saving me two hours a year – that is really something, I have to say, I would never expect I would be using this meter, but it's great! I'm on serious reducing variability mode as well, so I like the ketone check to test quickly anything over 250. On the pharma front, CDEs appear very excited about Byetta – the scientific theatre on day one was packed and as many CDEs (500-plus) were turned away as found seats. I hadn't been able to pre-register for symposia and the rep laughed at me when I mentioned how much I'd love to attend that one. I pressed, saying someone would not show up! (Felt like I was at the United counter.) "Okay, miss [love that – ed. note], miss, there are nineteen corporate symposia. Over half are sold out, but we can get you in to any of them except that one - you look serious, and I love your Mac. But so many would be upset, there are lines and lines of people that are on the wait list! Yes, I can get you into any of them except Incretin-Based Therapies, Achieving Better Glycemic Control. What is an incretin? Biata.com? How do I spell that? I need to give that to my uncle. No, I can't get you into that. One woman was crying earlier today because she couldn't get in – these are the rules, you must sign up early!' Luckily we did get in and the pitch was high – Drs. John Buse and Daniel Drucker (of glucagon.com fame) and CDE extraordinaire Dr. Linda Siminerio were an excellent team and we realized again – not everyone has even heard of these new drugs! Look for more on AADE in our September issue and in the meantime, for nightly commentary from AADE, please see our blog at www.diabetescloseup.com.*

*By way of background for this issue - we reckon heaps of opportunities exist in metabolic disease – so, we've been working hard on learning more about the area this year. In this issue, we highlight major lessons learned from the First International Conference on Pre-Diabetes in Berlin in April and the Obesity Drug Development Summit in Philadelphia in July – the latter of which was co-sponsored by Close Concerns. We've got an amazing special report on latter by Bernice Welles, M.D, former Venture Partner at MPM Capital and now VP of Development at DiObex. To add more to the metabolic disease arena next issue - I've just returned from some happy weeks in Australia, where I had the incredible opportunity to interview Dr. Paul Zimmet, renowned Foundation Director of the International Diabetes Institute in Melbourne. He was instrumental in planning the Berlin meeting, which was quite something, as you will read!*

*–by Kelly L. Close*

**T h e L o n g e r V e r s i o n**

## 1. Top Ten Themes from the First International Congress on Prediabetes and the Metabolic Syndrome

*This meeting took place in Berlin April 13-16, 2005. Nearly 2500 delegates from 85 countries attended and 450 abstracts were presented orally or as posters.*

**#1. Earlier diagnoses needed…but of *what* exactly?** On the first day of the meeting, Prof. Rury Holman, one of the driving forces and principal investigators of the UKPDS, drove home the point in not one but *two* presentations that earlier diagnoses of all manifestations of dysglycemia are required. Yet earlier diagnoses are possible only if we know what we are attempting to diagnose….

- *How do we even define prediabetes?*
  - The term "prediabetes" has a long and turbulent history. First coined in the 1960s, WHO abolished the term in 1980 in an attempt to prevent "negative labeling." People who would have been "prediabetic" were then described as having a "previous/potential abnormality of glucose tolerance." Impaired glucose tolerance (IGT) was first described in 1979-80 and impaired fasting glucose in the late 1990s.
  - The term "prediabetes" came back in March 2002 when US HHS Secretary Tommy Thompson warned Americans of the risks of "prediabetes," a condition affecting nearly 16 million Americans. HHS and ADA had been using "prediabetes" to describe formal diagnoses of IGT or IFG.
  - Though prediabetes is an established term, its treatment remains controversial but by 2025, nearly half a billion people around the world are expected to have it, according to projections by the International Diabetes Federation
    - India will by far lead the world absolute number of cases of IGT and the Middle East will see a lot of it too.
- *How do we define the metabolic syndrome*?
  - Professor Sir George Alberti described the metabolic syndrome as "a cluster of risk factors for diabetes and CVD" but there has been no consistency or universal agreement on the WHO definitions issued in 1997
  - ATP-III definition in 2001: three or more of central obesity, hypertriglyceridemia, low HDL, hypertension, and IFG
    - CC Note: ATP-III was sponsored by the National Cholesterol Education Program, so this definition not decided primarily by endocrinologists
  - IDF Consensus from 2004: BMI, waist/hip ratio, waist circumference
    - Central obesity is key. Waist girth has to be ethnicity-specific because it is unreasonable to use the same anthropometric measures when body types are so different
    - Raised triglycerides, low HDL, elevated blood pressure, dysglycemia
    - Insulin resistance not to be measured because this is too difficult to do in routine care
    - We need a practical guide that is usable worldwide
  - IDF consensus definition of metabolic syndrome (2005): central obesity plus any two of: raised triglycerides (>150 mg/dL); low HDL: <40 mg/dL for men, <50 mg/dL for women; blood pressure >130 mm/Hg systolic OR >85 mm/Hg diastolic or current treatment for high blood pressure; IFG or pre-existing diabetes or IGT/abnormal glucose values >100 mg/dL
  - Is there a gold standard against which to compare everything? No agreement.

        - No prospective trial evidence that treating the metabolic syndrome prevents CVD and diabetes although indirect evidence suggests this is so.
    - *What to treat in prediabetes?*
        - Insulin resistance, central obesity, dyslipidemia, hypertension, hyperglycemia but Alberti doesn't think we'll get around to polypills with six different components.

**#2. Even people with normal glucose tolerance who have cardiovascular disease (CVD) should be watched for the Metabolic Syndrome and prediabetes**. People who have normal glucose tolerance can have lost about 60% of beta-cell function. The cut-off for IGT is completely arbitrary, and as we get better at making these measurements, we can get a better idea of when we should intervene.

- The NAVIGATOR trial is the only IGT trial to examine directly the potential for reducing CVD risk, in addition to reducing the risk of developing type 2 diabetes.
- Started in 2001, the trial has a follow-up of five to seven years, and published results are expected in 2008

- The culprit of diabetic dyslipidemia is the elevation of large VLDL1 particles that are markedly reduced by fenofibrate.
    - FIELD will be a landmark study in providing definitive evidence for CHD prevention in diabetes with special application to showing the effect of PPAR agonism on lipid levels
- Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial to see if ACE-inhibition and TZD treatment can prevent the progression to diabetes of patients with IFG or IGT
    - Ramipril: ACE-inhibitor (15 mg). Already a proven cardioprotective drug.
        - Rosiglitazone: TZD (8 mg)
        - Started July 2001, results to be available early 2007.
    - ORIGIN study will examine the glycemic and cardioprotective effects of treatment with insulin and omega-3 fatty acids on patients at high risk for CVD who also have IFG or IGT or diabetes
        - Glargine and omacor; results expected 2008
    - Trials in which the primary outcome is diabetes
        - NAVIGATOR (valsartan, nateglinide), DREAM (ramipril, rosiglitazone), EDIT (metformin, acarbose), FHS (gliclazide), NANSY (glimepiride), CANOE (rosiglitazone + metformin), PIPOD (pioglitazone), ACT NOW (pioglitazone), Indian DPP2 (pioglitazone)

**#3. Incretin hormones.** Incretin hormones are quite possibly the most promising tools for diabetes management to be discovered since insulin. By modulating and bolstering the endocrine system with these agents, we may restore euglycemia with less risk of hypoglycemia and *desirable* side effects like moderate weight loss.

- *Jens Holst: 70% of post-glucose challenge insulin secretion is due to the incretin effect*
    - GLP-1 restores beta cell responsiveness to glucose in type 2 diabetes patients, but the sensitivity of the beta cells in people with diabetes is much less than that of non-diabetic patients. Thus, diabetic beta cells need a boost with GLP-1.
    - Restoration of the incretin effect by exogenous GLP-1 may normalize or improve metabolism
    - Amplification of endogenous GLP-1 may have a similar effect.
- *E. Standl: Despite major advances in treatment of type 2 diabetes, only a minority of patients meet glycemic targets over the longer term*.
    - Beta cell mass is significantly decreased in obese patients with IFG or type 2 diabetes (greater reduction in type 2 diabetes).
    - Insulin secretion deficit increases progressively. Obesity leads to insulin resistance.

- *M Nauck: GLP-1 is a promising therapeutic area for type 2 diabetes and prediabetes*
  - GLP-1 can stimulate insulin secretion (in response to glucose), restore rapid first-Phase respond to glucose bolus, restore the incretin effect, suppress glucagon (glucose-dependent), increase beta cell mass (in animals), reduce appetite, increase satiety, and reduce calorie intake (but no immediate effect on insulin sensitivity)
  - GLP-1 has a half-life of about two minutes, and for long-term treatment, GLP-1 derivatives (incretin mimetics) with a longer half-life must be used.
  - The other alternative is to prevent the proteolytic degradation of endogenously secreted GLP-1 with DPP-IV inhibitors.
    - Although no clinical studies with the aim of preventing diabetes are available, DPP-IV inhibitors appear attractive for this purpose

**#4. Rimonabant for metabolic syndrome.** Rimonabant has been mentioned as a treatment for smoking as well as for diabetes because of its potent effects on the brain and the body. New research indicates that it may have a place in the treatment of the metabolic syndrome as well. Several audience questions referred to the potential for unanticipated effects because rimonabant receptors spread throughout the body. Yet these questions were somewhat sidestepped by, researchers who replied that their studies did not set out to study side effects!

- *D. Greene (Sanofi-Aventis): Endocannabinoid (EC) system is a new target for multi-risk management*
  - EC system modulates feeding behavior and hepatic and adipocyte lipogenesis
  - EC system upregulation in chronic obesity promotes weight gain, lipogenesis, insulin resistance, dyslipidemia, and glucose intolerance
  - Response to CB-1 receptor antagonism may help refine both the definition and treatment of metabolic syndrome
  - Rimonabant promotes weight loss, improves HDL and triglycerides, and improves insulin sensitivity independent of weight loss
  - Rimonabant induces metabolic effects independent from food intake (i.e., food metabolism changes)
  - Rimonabant stimulates adiponectin production (key regulator of fat and glucose metabolism). Obese subjects and subjects with T2D have decreased levels of adiponectin.
- *J. P. Despres: Effects of Rimonabant on Metabolic Syndrome—Recent findings from the RIO Trial Program*
  - Rimonabant Phase 2 program (seven studies including over 13,000 patients)
  - RIO Program in Obesity (over 6600 patients enrolled); results of RIO-Diabetes will be presented later in 2005. (CC Note: RIO-Diabetes data were presented at the ADA in early June)
  - RIO-Lipids
    - Changes in weight and waist circumference.
    - Placebo group compliant, lost some weight but rimonabant 5 mg caused more weight loss and 20 mg rimonabant reduced waist circumference by 9 cm and weight by 8 kg.
    - Glucose tolerance significantly improved (reduced by 9%)[DOES THIS NEED CLARIFICATION?] after one year with rimonabant 20 mg, insulin response improved as well (insulin sensitivity increased).
    - No change in LDL cholesterol from rimonabant after one year of treatment. However, there was a shift in the proportion of small LDL particles to LDL particles that was beneficial.
    - Adiponectin is a good cytokine! The reduction in adiponectin levels is associated with increased visceral fat - Rimonabant improves this.

- RIO-Europe validated RIO-Lipid's reductions in waist reductions, increase in HDL, reduction in triglycerides
    - At two years, rimonabant takers are able to maintain their waist circumference reduction compared to the placebo group.

**#5. Preventing or delaying diabetes onset by lifestyle.** While the Diabetes Prevention Program showed that lifestyle interventions are more effective in terms of preventing progression to diabetes in high-risk patients than pharmacological therapy, lifestyle interventions are often expensive and problematic to implement. Nevertheless, lifestyle interventions cannot be abandoned.

- *F. Kaufman: Community-based approaches can help reduce obesity among children*
    - As usual, Dr. Kaufman's talks are moving. She discussed a wide range of items, including communications, community programs, changing eating habits, more physical activity, programs in schools and community centers, environmental change, sidewalks and bike trails, neighborhood safety, and urban planning.
    - AAP Policy Statement: calculate and plot BMI yearly, no more than 2 hours of sedentary behavior per day, promote healthy eating patterns, promote physical activity of one hour per day, encourage, support, and protect breastfeeding, target children in schools
    - School-based programs can decrease soda consumption as well as sedentary activities
    - Federal actions: Child Nutrition Reauthorization Act 2004
    - WHO 2004 Global Strategies on diet, physical activity, and health
- *C. Caprio: 20-30% of all new diabetes cases in adolescents are type 2*
    - In adults, natural history of type 2 diabetes occurs over seven to ten years: NGT→IGT→type 2 diabetes. Key question: Is this pattern the same in children?
    - Multiethnic study of 500 obese children
        - 24% of obese pre-adolescents with IGT
        - 20% IGT for obese adolescents, 4% silent diabetes
        - Key finding: IGT and the metabolic syndrome are highly prevalent among children and adolescents with marked obesity; insulin resistance is the most important risk factor linked to IGT
    - Prospective longitudinal study of IGT in childhood obesity ("AIMS") to examine the role of insulin resistance and beta cell function in the transition from NGT to IGT/type 2 diabetes.
        - Childhood obesity → increased visceral/subcutaneous fat ratio, increased intramyocellular lipids, low adiponectin → insulin resistance → hyperinsulinemia → beta cell failure→ prediabetes/diabetes
        - Progression from IGT to diabetes is very quick in children.
- *T. J. Wilkin: Earlybird study – which children develop insulin resistance and why?*
    - 300 children and their parents are currently enrolled in the UK, recruitment began in 2000.
        - Four stages exist throughout puberty, in very narrow age spread—it is possible to see changes related to age, taking fasting blood samples in subjects as young as *five* years.
        - Measuring insulin, glucose, triglycerides, cholesterol, PCV, urate, and more, archiving DNA.
    - Linear rise in adiposity in boys and girls, correlations between skinfolds and insulin resistance (over five to eight years), but these correlations were cross-sectional, and we can't assume that insulin levels will rise just because adiposity rises. Surprisingly, from five to seven years of age there is a fall in insulin resistance associated with a rise in adiposity. HDL cholesterol rising.

- Progressive increase in blood glucose shown (inconsistent with decrease in insulin resistance)

**#6. Preventing or delaying diabetes onset using TZDs.** For several years it has been speculated that progression from prediabetes or the metabolic syndrome to diabetes might be prevented by TZD use. Now the results are coming in….

- *T. Buchanan: What are the effects of TZDs on progression to diabetes? The PIPOD trial*
  - Results not published yet
  - PIPOD followed up on TRIPOD, which had used troglitazone, with the same subjects
  - Data from 86 women who entered without diabetes, on drug for three years, off drug for six months.
  - Rate of incidence of diabetes in pioglitazone group was about the same as with troglitazone (4.6% per year).
  - Did pioglitazone alter the course of beta-cell function?
    - Pioglitazone treatment associated with a relatively low incidence rate of diabetes
    - Pioglitazone stabilized declining beta-cell function in women who had been losing function on placebo.
- *R. A. DeFronzo: Can pioglitazone prevent or delay progression to type 2 diabetes? The ACT NOW trial*
  - Prospective trial going on with IGT patients taking pioglitazone to see if we can prevent/delay progression to type 2 diabetes.
  - Randomized, double-blind, placebo-controlled, 45-month study involving 600 IGT subjects
    - 340 people have entered to date.
    - Waist circumference: 110 cm for men/103cm for women
    - Mean BMI 34, mean A1C 5.5%, FPG 105 mg/dL, 2hPG = 166 mg/dL
  - Primary endpoint: development of diabetes, based on OGTT or FPG [EXPLAIN "ENDPOINT" HERE OR IN FOOTNOTE???]
  - Secondary endpoints: improvement in glycemic control, improvement in beta-cell function, improvement in insulin sensitivity
  - Results to be presented in 1.5-2 years

**#7. Postprandial hyperglycemia and the importance of early insulin use.** The primary defect of insulin secretion in type 2 diabetes is first-phase insulin response at mealtimes, which leads to postprandial hyperglycemia that may exacerbate beta-cell dysfunction. Initiating insulin early in the disease state may preserve beta-cell function longer and is correlated with reduced risk of long-term complications.

- *Ceriello: STOP-NIDDM showed that reduction of postprandial hyperglycemia (PPHG) will prevent diabetes and CVD/hypertension*.
  - Managing PPHG is enough to moderate risk factors for developing future CV disease.
  - Recent studies on type 2 diabetes in animal models suggest that the progressive reduction of islet beta cells is associated with excessive oxidative stress. When hyperglycemia is allowed to continue, glucotoxicity results
  - PPHG causes endothelial dysfunction that leads to atherosclerosis
- *K. Malmberg: DIGAMI 2 confirms that glucose level is a strong independent predictor of long-term mortality in patients with AMI and diabetes.*
  - DIGAMI 2 did not support the primary, secondary, or tertiary hypotheses but the overall mortality was much lower than expected, especially in the conventionally treated group—close to non-diabetic rates.

- DIGAMI 1 and 2 suggest that type 2 diabetes patients should have intensive glucose control after AMI. This probably can be accomplished by treatments other than insulin as long as glucose control is efficient. Meticulous concomitant treatment is important.

**#8. Cost-effectiveness, government roles, and reimbursement systems.** While it's all well and good to emphasize tight control of blood glucose levels as a goal in every case of dysglycemia, this is easier said than done in the many places and situations in which reimbursement systems and public health authorities are not equipped to deal with the costs of caring for people with diabetes.

- *P. Zimmet: 2004 statistics on IGT indicate 97 million known cases, 97 million undiagnosed cases*
  - Leading regions for IGT prevalence: old Soviet states, Middle East, Nauru.
    - Numerically, India, and China lead the pack.
    - In the US, diabetes cost $20 billion in 1987, $132 billion in 2002, and it's growing
    - Annual healthcare costs: non-diabetic individual: $2,560; diabetic individual: $13,243; main burden of costs from macrovascular disease
- *A. Porath: Insurance payers cover morbid obesity and diabetes, but not metabolic syndrome and being overweight.*
  - Competing priorities: pre-hypertension is one of these: risk for heart attack, heart failure, and kidney disease in the hypertensive population, aggressive lipid treatment.
- *A. J. Palmer: Interventions that prevent or delay diabetes substantially improve diabetes and are usually either cost-saving or cost-effective.*
  - Costs of Diabetes in Europe (CODE-2) study: Direct medical costs of type 2 diabetes in eight European countries amounted to 29 billion Euros per year
  - Direct and indirect costs. of diabetes in the US projected to reach $192 billion by 2020 (*Diabetes Care* 2003)
  - US QALY threshold is about $50,000 (£30,000 in the UK)
  - DPP group: USA Modeling Analysis: cost per QALY was $1,124 in intensive lifestyle changes group and $31,286 in metformin group, relative to control but there was a very high cost of metformin assumed.
  - Cost-effectiveness interventions differ from country to country and depend on medications, healthcare unit costs, costs of treating diabetes complications, and other factors.
- *N. Finer: PROCEED is a novel paradigm for collecting data to assess the impact of being overweight and obesity (especially abdominal obesity) on health and health economics*.
- *P. H. Bennet: "Diabetes could become the AIDS of the 21st century…The importance of diabetes prevention cannot be underestimated."* – Prof. Sir George Alberti, IDF President
  - Excess deaths attributable to diabetes in 2000: 3.16 million (5.4% of all deaths) if people with diabetes had the same mortality as non-diabetics, which they do not.
  - If you're obese, you are still much better off in terms of incidence of diabetes if you are highly active
  - Obesity, diabetes, and related CVD are environmentally caused diseases of lifestyle.
  - Sixty-two percent of Americans support a law requiring restaurants to put nutritional information on the menu.
- *P. Lefebvre: diabetes poses a significant threat to economic development, and this is not sufficiently recognized.*
  - Economic development leads to increased levels of diabetes and other non-communicable diseases, which lead to, increased healthcare expenditures for families, lower investment, and lower productivity.

- Funding for non-communicable diseases at WHO: three and one-half percent of the WHO budget is spent on non-communicable diseases.

**#9. Is monotherapy possible?** For years, the holy grail of type 2 diabetes treatment has been the "magic bullet," one pill to combat all of the pathophysiologies common in diabetes, including but not limited to hypergylcemia, hypertension, hypercholesterolemia, and hypertriglyceridemia. This goal is crucial but has been elusive in large part because it has proved very difficult to create an agent that can address at least two of these dysfunctions without causing tumors in mice (dual PPAR-agonists) or ulcers in people (halofenate). Drs. Vosatka and Lebovitz shared their perspectives on the prospects for a complete one-pill treatment for the constellation of factors that precede and contribute to diabetes.

- *Vosatka: metabolic syndrome is similar to Cushing's Syndrome, which is caused by excess glucocorticoids.* Shared features: abdominal obesity, hypertension, insulin resistance, dyslipidemia but in metabolic syndrome people do not have abnormally elevated glucocorticoid levels.
  - Hypothesis: in inhibiting HSD1, we can lower intracellular cortisol concentrations and treat MS.
  - Pharmacological inhibition of 11-beta-HSD 1 appears to be a single mechanism that can affect multiple features of metabolic syndrome. This is true at least in mouse models.
- *H. Lebovitz: mixed PPAR-agonists and drugs that increase intracellular insulin action are promising candidates for the treatment of diabetes, but they are not without their limitations*
  - PPAR-gamma agonists: increase fatty acid oxidation, decrease apo C3 levels, inhibit inflammatory cascade
  - PPAR-delta agonists promote reverse cholesterol transport
  - Dual alpha and gamma PPAR action addresses multiple risk factors in type 2 diabetes—would be therapeutically better and would target more issues.
    - Muraglitazar (Bristol-Myers Squibb/Merck) completed Phase 3 and is being evaluated by the FDA – significant further glucose lowering in combination therapy (glyburide or with metformin); substantial impact on lipid levels
      - Weight gain and mild to moderate peripheral edema consistent with currently available PPAR gamma activators
  - Problem with dual-PPAR agonists: need to see more data to see whether side effects outweigh benefits.
  - Mitochondrial anti-oxidants—a new promising area because primary mitochondrial abnormality is associated with insulin resistance.
    - Metabolic syndrome results in oxidative stress products.
  - AMP-activated protein kinase and PKC-B inhibitors have great potential

**#10. <u>Marked variability of waist circumference exists at any given BMI.</u>** <u>We have recognized for some time that BMI is not necessarily the best indicator of health status. The finding that waist circumference can vary at a given BMI is critical to our understanding of phenotypes of obesity and our techniques for assessing risk for diabetes, prediabetes, and the metabolic syndrome on an individual basis.</u>

- WHO and IDF released at the conference new diagnosis criteria for the metabolic syndrome specifying different waist circumference measures for various ethnicities:
  - Europids: males ≥94 cm, females ≥80 cm
    - The ATP-III criteria, which allow for men to have a waist circumference of up to 102 cm and women to reach 88 cm before diagnosis of metabolic syndrome, are likely to remain in clinical use in North America
  - South Asians: males ≥90 cm, females ≥80 cm
  - Chinese: males ≥90 cm, females ≥80 cm

        - Japanese: males ≥85 cm, females ≥90 cm
    - *N. Finer: Those with abdominal obesity have more symptoms, greater knowledge of co-morbidity, and greater healthcare consumption than overweight/obese without abdominal obesity.*

*--By Bradford Lee and Melissa P. Ford*

## 2. Obesity Drug Development Summit

**The Obesity Drug Development Summit, sponsored by the Center for Business Intelligence, took place in Arlington, Virginia on July 21-22.** About 70 attendees, the majority from academia and industry and several others from government agencies (such as the NIH), turned out. A main theme of the conference was the explosion of therapeutic targets for obesity treatment and key preclinical data on several compounds were presented. It remains to be seen what will happen in human trials of several early-stage drug targets – this will be interesting to monitor but will probably not have much clinical impact before the end of the decade.

**Day One was moderated by Rebecca Taub, Ph.D.,** VP-Research, Hoffman-La Roche. Dr Taub provided a nice overview of the conference agenda:

- Forecasts and FDA Guidance
- Neuroendocrine Regulation of Energy Balance
- The Role of Peripheral Tissues in the Control of Energy Balance
- Targeting Type 2 Diabetes and Insulin Resistance

**Day Two was moderated by Barbara Hansen, Ph.D., Professor of Physiology, University of South Florida International Institute for Biomedical Research.** Dr. Hansen presented a comprehensive review of the effects of PPAR agonists (α,γ,δ and various combinations thereof) in primate models of "diabesity." A key question that she discussed was whether PPAR agonists are *calorie restriction mimetic agents*.

**While surgical interventions got virtually no airtime, gastric bypass was cited as the current gold standard**. Overall, the conference reflected a mixture of hope and frustration among attendees. There was an upfront acknowledgement that monotherapy is not effective enough, as monotherapy using currently marketed pharmacological interventions and data from drugs in clinical trials indicates that such drugs have yielded only modest weight loss and contributed major side effects! On the plus side, modest weight loss has a beneficial impact on the metabolic syndrome – specifically, it helps prevent it altogether! However, physiological pathways related to obesity are complex and demand more intervention than monotherapy can provide. Combination therapy will undoubtedly be the wave of the future. Many targets still await clinical validation; safety and efficacy in rodent models of obesity may not be predictive of safety and efficacy in obese humans (e.g. beta 3-adrenergic receptor agonists).

**Rodolfo Valdez, Ph.D., from the Centers for Disease Control and Prevention, provided an in-depth discussion of the obesity pandemic**. The epidemiology of obesity never ceases to amaze. There are *300 million* obese individuals in the world, 20% of them US residents. Shockingly, obesity has begun to co-exist alongside malnutrition in the developing world. At one end of the spectrum, people die from lack of food, while at the other end they are killing themselves through overnutrition.

**Eric Colman, M.D., from the FDA's Division of Metabolic and Endocrine Drug Products, presented a historical perspective on the regulation of obesity drugs in the US.** At present, the FDA is in the process of revising its guidelines for the development of weight control drugs. The process kicked off in January 2004 with a request for public comment. The FDA received 17 responses, mostly from industry.

The overall tenor of the comments was (unsurprisingly) to make the guidelines less restrictive, with two specific requests:

- The Agency broaden inclusion criteria for obesity by decreasing the lower limit of BMI to 25 $kg/m^2$ (rather than 27 $kg/m^2$ with co-morbid conditions or 30 $kg/m^2$ without co-morbidities)
- Eliminate the second year of open-label studies and reduce the number of subjects required from 1500 at one year to 300-600 subjects at six months and 100 subjects at one year.

**An Endocrine and Metabolic Drugs Advisory Committee meeting was held in September 2004**. Additional issues investigated were run-in phase length (currently six weeks) and magnitude of effect that is clinically significant (currently a loss of 5% of initial body weight). Release of the revised guidelines is projected for the end of 2005. It sounds as though the BMI cutoff, overall size of the pivotal program, and magnitude of efficacy are unlikely to change. Metabolic syndrome is not likely to receive indication status in the near future. Large clinical outcomes trials – to evaluate risk for cardiovascular disease, for example – are encouraged either before or after approval.

**Company presentations on compounds close to approval**: Given the relative dearth of clinical stage compounds in development, only four companies presented clinical stage compounds:

- Sanofi-Aventis (Douglas Greene, VP-Corporate Regulatory Development): Rimonabant. This selective cannabinoid-1 (CB1) receptor antagonist has been studied in more than 6500 overweight and obese subjects in Phase 3 trials. It is currently under regulatory review in the US. and the EU. Dr. Greene pointed out that the CB1 receptor is a young target and that the basic science is marching forward in lock step with late stage clinical development**.** New research (Osei-Hyiaman et al., *J. Clin. Invest.* 2005; 115: 1298–1305) indicates that activation of CB1 plays a dual role in the development of diet-induced obesity. In the liver, activation of CB1 results in increased serum lipid production and fatty liver. Stimulation of CB1 receptors in the hypothalamus may lead to an increase in food consumption. Targeting both of these pathways with CB1 receptor antagonists could promote sustained weight loss and favorable serum lipid profiles in obese patients.

  The RIO-Europe study, a two-year, multicenter, randomized, double-blind, placebo-controlled trial, enrolled over 1500 obese patients. During a one-month run-in period, before being randomized to one of three parallel treatment arms (placebo, 5 mg/day rimonabant, or 20 mg/day rimonabant), patients were placed on placebo and a hypocaloric diet (600 kcal/day deficit). Patients receiving 20 mg/day rimonabant lost an average of 8.6 kg of body weight after one year, compared with 4.8 kg lost by patients on the 5 mg/day dose and 3.6 kg lost by patients on placebo. Secondary benefits included increased adiponectin levels and a decrease in A1C of 0.7%. It should be noted that these patients were concomitantly on hypoglycemic medications, so rimonabant was not necessarily completely accountable for the decrease. It was reported that these benefits exceeded improvements that could be attributed to weight loss alone, thus suggesting that there is a direct, independent effect of rimonabant on these parameters.

  In addition, there were beneficial changes in levels of HDL, triglycerides, and C-reactive protein, as well as a decrease in the proportion of the atherogenic small dense LDL particles. Dropout rates were similar amongst all groups, and the adverse events were generally dose dependent. The most commonly reported adverse events at the 20 mg dose were nausea (13% vs 5% on placebo) and dizziness (9% vs 5% on placebo). Anxiety and depression were seen in less than 5% of patients and Sanofi-Aventis claims that this is consistent with other obesity trials; patients using anti-depressants were excluded from enrolling in the trials. Rimonabant is also effective as a smoking cessation aid. In the STRATUS-US study, a 10-week study that enrolled 787 long-term smokers, who are either overweight or obese; these subjects receiving rimonabant lost an average

of one pound each, compared with a gain of one pound and three pounds in overweight and obese smokers, respectively, in the placebo group.

- Amylin (Christian Weyer, Sr. Director of Clinical Research): PYY 3-36 and Pramlintide (Symlin). Amylin is investigating bioactive peptide hormones as a pharmacologic therapy for obesity. Their approach is to start out by screening ligands in animal models. One downside is that these peptides are administered by injection, but the touted benefits are increased safety due to short circulation times, limited exposure around mealtimes, and (partly as a result) a lower likelihood of late stage failure. PYY 3-36 is secreted by entero-endocrine cells in the small and large intestines. Of note, PYY and other satiety hormones are elevated following Roux-en-Y gastric bypass surgery. In 2003, Batterham et al. (*N Engl J Med* 2003; 349: 941-8) reported results of a small clinical trial of PYY 3-36 in which 12 obese and 12 lean subjects were studied in a double-blind, placebo-controlled, crossover study. Caloric intake during a buffet lunch offered two hours after PYY infusion was decreased by 30% in the obese subjects ($p = <0.001$) and 31% in the lean subjects ($p = <0.001$). While it is reported that a number of other groups have failed to reproduce Batterham's results, Amylin claims that this peptide consistently produces weight loss. A 10 patient Phase 1 study has been completed, and this program continues in Phase 1 testing.

  Recently approved as an adjunct therapy to mealtime insulin in patients with diabetes, pramlintide (Symlin) is a glucoregulatory peptide whose anorectic effects appear to reside within the central nervous system. Numerous trials with pramlintide have shown a dose-dependent weight loss, which was maximal (2 kg) at the 150 mcg three times daily dose. Results of a 16-week Phase 2 study of 204 obese patients have also been reported. Dosage was titrated and 90% of patients were able to tolerate doses of 240 mcg three times daily. Mean weight loss was 3.5 kg (3.6% of bodyweight). The question arises as to whether nausea, a common side effect of pramlintide, is directly linked to the weight reduction. Apparently, nausea is transient during dose titration and improves after the titration period.

- Alizyme (Richard Palmer, CEO): Cetilistat. Alizyme appears to have the second-in-class lipase inhibitor. Roche marketed the first-in-class lipase inhibitor, Xenical® (Orlistat), which produces modest weight loss but also can cause oily stools and anal leakage. These side effects are related to its mode of action, the inhibition of dietary fat absorption. Alizyme has completed a Phase 2b trial of cetilistat in obese patients. This 12-week trial was conducted in five European countries. Average weight loss was comparable across the three dosage groups tested (60 mg, 120 mg, and 240 mg three times daily) and, based on published data, was similar to weight loss with 120 mg three times daily of Xenical®. Cetilistat appears to have an improved gastrointestinal adverse event profile compared with Xenical, particularly in terms of flatus with discharge and oily spotting. The reason for this more favorable side effect profile is unclear. Alizyme plans to initiate a Phase 3 program and will move forward with a dose of 80 mg three times daily.

- Arena Pharmaceuticals (Dominic Behan, Ph.D., CSO and Sr. VP): APD356. APD356 is a selective 5-HT2c receptor agonist. This receptor was also the target of the notorious appetite suppressants fenfluramine and dexfenfluramine, but those compounds also interacted with the 5-HT2b receptor, which is the known link to the cardiac valvular side effects caused by these drugs. Also noted was that 5-HT2a side effects include hallucinations in humans. Preclinical studies demonstrated that Arena's compound APD356 has a high affinity and specificity for the 5-HT2c receptor, with approximately 15-fold and 100-fold selectivity over the 5-HT2a and 5-HT2b receptors, respectively, and no pharmacologic activity at other serotonin (5-HT) receptors. Hence, the belief is that APD356 administration is unlikely to result in undesirable side effects associated with non 5-HT2c receptor activation. The results of a 28-day Phase 2a study were presented at the

summit. This study was performed in 352 patients each with a BMI between 30 and 45 kg/$m^2$. Patients were instructed to remain on their usual regimens and to avoid caloric restriction or increased exercise. Doses of 1, 5, and 15 mg daily were tested and very modest decreases of weight were seen in the 5 and 15 mg dose groups as compared with placebo. Statistical significance was reached in the 15 mg dose group ($p = 0.0002$), where the mean weight reduction was 1.3 kg, compared with a mean weight reduction of 0.3 kg in the placebo group. Echocardiography was performed to look for valvular lesions, but none were detected. Side effects of 5-HT2a appear to be dose-limiting. In the upcoming placebo-controlled Phase 2b study, doses of 10 mg and 15 mg daily, as well 10 mg twice daily, will be tested. The plan is to enroll approximately 100 patients in each group. Arena Pharmaceuticals anticipates beginning a 12-month Phase 3 trial in mid-2006 and a potential launch in 2009.

Athersys, Inc. (Alain Stricker-Krongrad, Ph.D., Sr. Director of Pharmacology) also presented information on their 5-HT2c receptor agonist. They are completing IND-enabling pre-clinical studies and expect their drug to be in clinical studies in early 2006. Their lead compound, ATH-88651 (listed as ATHX-105 on their website), appears to have good penetration into the brain and to be selective for the 5-HT2c receptor.

A number of other companies reported on their discovery/ pre-clinical programs:

- Merck (Alison Strack, Ph.D., Sr. Research Fellow) is working on melanocortin 4 receptor (MC4R) agonists. MC3R and MC4R are members of a family of five G-protein-coupled receptors and act in the central nervous system to regulate food intake and energy homeostasis. MC3R and MC4R knockout mice are obese, but only the MC4R knockout mice show hyperphagia (excessive eating). MC4R has been demonstrated to be the principal melanocortin receptor for regulation of food and water intake. Inactivating mutations of MC4R causes obesity both in mice and in humans.

- MC4R has also been implicated as a modulator of erectile function: Palatin Technologies is reportedly in pre-clinical development of a selective MC4R agonist for obesity and in Phase 2 trials for male and female sexual dysfunction with its melanocortin agonist PT-141.

- Johnson & Johnson's Pharmaceutical Research & Development group (Monique Berwaer, Ph.D., Principal Scientist and Metabolic Diseases Team Leader) appears to be broadly interested in the obesity area. Dr. Berwaer provided an overview of the scientific rationale for three targets: ghrelin, 11 beta-hydroxysteriod dehydrogenase-1, and diacylglycerol acyltransferase.

    - Ghrelin is a peptide hormone, produced mainly in the stomach that plays an important role in meal initiation and food intake in rodents and humans. Ghrelin levels are elevated in individuals with Prader-Willi Syndrome, a genetic disorder that causes constant hunger and severe obesity. Conversely, ghrelin levels are decreased in obese individuals without Prader-Willi Syndrome compared to individuals of healthy weight. Noxxon Pharma AG (presented by Sven Klussman, Ph.D., CSO) presented their discovery platform and stated that they are developing a ghrelin antagonist, NOX-B11, which is an aptamer that has been studied in rodent models and reportedly has a clean toxicology profile. Noxxon is seeking a co-development or outlicensing deal.

    - The second topic covered in the JNJ presentation was 11 beta-hydroxysteroid dehydrogenase-1 (11-β-HSD1) inhibition. Overexpression of 11ß-HSD1 in murine adipose tissue results in glucocorticoid receptor (GR)α overexpression, central obesity, and insulin resistance, while the 11-β-HSD1 knockout mouse is protected from

developing obesity. Numerous companies have programs that target 11-β-HSD1 inhibition. Biovitrum/Amgen was reported to have stopped developing their lead compound of this type because of lack of efficacy, but a second compound is currently under investigation. Tissue specificity (e.g., liver vs. adipose tissue) is likely to be a key issue.

- The third approach discussed was the selective inhibition of diacylglycerol acyltransferase (DGAT) mediated triglyceride synthesis. DGAT-1 deficient mice are viable and demonstrate alternative pathways of triglyceride synthesis. They have reduced tissue triglyceride content, diminished adipocyte mass and size, as well as increased insulin sensitivity and resistance to obesity. About half a dozen companies have programs targeting DGAT. Only rodent data have been generated to date, and there are no clinical stage programs.

- AdipoGenix discussed its discovery platform, which is focused on adipose targets. AdipoGenix researchers take subcutaneous, omental, and mesenteric fat from donors of various ages, ethnic backgrounds, and medical conditions. Preadipocytes are isolated and differentiated to form mature fat cells. Compounds are then screened for cytotoxicity and for their ability to induce ≥ 50% reduction of lipid content within the cells. Two small molecule leads have been generated by this method: AGX-0104 targets a transcription factor and AGX-0119 targets an enzyme. Both compounds are currently undergoing in vivo pharmacokinetic, toxicology, and efficacy testing in rodent models.

- Regeneron (Mark Sleeman, Ph.D., Director of Neural and Endocrine Biology) showed strong interest in metabolic diseases. Dr. Sleeman reported that Axokine (ciliary neurotrophic factor**)** continues to be in development for obese patients with type 2 diabetes, although no information is currently listed on the Company's website. Inhibition of type 2 SH2-domain-containing inositol 5-phosphatase ("SHIP2 lipid phosphatase") was cited as a target for obesity treatment, as such inhibition has been shown to increase insulin sensitivity in rodents.

- Galileo Pharmaceuticals (Sekhar Boddupalli, Ph.D., VP Discovery) is seeking to identify novel plant-derived anti-inflammatory compounds that modulate inflammatory pathways by inhibiting therapeutically relevant targets. Rather than directly target weight loss or hyperglycemia, this discovery program targets inflammation associated with obesity and metabolic syndrome.

- CombinatoRx, Inc. (Alyce Finelli, Ph.D., Scientist, Metabolic Disease Research) screens millions of drug combinations in search of mixtures that target multiple pathways in a disease network. Dr. Finelli provided a detailed presentation of the Company's proprietary method of screening drug combinations in cell-based assays modeling glucose uptake. An undisclosed combination product is in pre-clinical development for diabetes. Of note, neither of the compounds in the drug combination has previously been used to treat hyperglycemia.

Other potential targets of note (John Clapham, Ph.D. Associate Director, AstraZeneca):

- Fatty acid (FA) oxidation is decreased in obese muscle and is impaired after weight loss. This observation has led to the hypothesis that impaired FA oxidation may contribute to weight regain. A number of therapeutic approaches could be taken to increase FA oxidation and decrease FA synthesis. One such approach is the inhibition of acetyl-CoA carboxylase (ACC). This method results in inhibition of FA synthesis and stimulation of fatty acid oxidation, potentially improving the cardiovascular risk factors associated with metabolic syndrome.

- Inhibition of glycerol-3-phosphate acyltransferase (GPAT) is another possible approach to treating obesity. GPAT may regulate β-oxidation, and when mitochondrial GPAT is over-expressed in the liver of adult mice, hepatic steatosis develops.

Ultimately, the conference reinforced that, apart from compounds from Sanofi-Aventis and Amylin, there are few new clinical compounds of note that could be used in the next couple of years. However, targets are promising and we will keep a watchful eye on this area, as the need to treat obesity is obviously huge and moving only one direction at present.

*--Special report by Bernice Welles, M.D. Dr. Welles is Vice President of Development at DiObex, a San Francisco based biotechnology company founded in 2003 to develop novel products for the treatment of metabolic diseases. Before joining DiObex, Dr. Welles was a Venture Partner at MPM Capital. Dr. Welles previously spent eight years at Genentech, Inc., as Vice President of Product Development, with responsibility for all development projects and portfolio planning. She is board certified in both Internal Medicine and in Endocrinology. Dr. Welles will be speaking on obesity and DiObex' development program at the 2nd Annual World Obesity & Weight Loss Congress, Sept 12-13, 2005 (Washington, DC).*

### 3. A Look Back: Michael Brownlee's Banting Address, ADA 2004

***DCU will review the 2005 Banting Medal address by Jeffrey Flier, M.D. in our September issue – for a detailed update on the 2005 ADA, please see our last issue of DCU. Flier's address during the 2005 ADA focused on the regulation of appetite and obesity by the central nervous system. In this issue, we go back to 2004's Banting Medal address by the noted scientist Dr. Michael Brownlee.***

One of the most frightening aspects of the diabetes is the development of complications that occur with prolonged hyperglycemia: vision loss, kidney failure, and peripheral neuropathy. Unfortunately, although these areas have become major areas of focus for pharmaceutical companies, there are few good treatments for these complications, particularly in the latest stages, and the area is fraught with disappointment[1]. It is still agreed that by far the best treatment for avoiding complication development is through prevention through tight control of blood glucose levels over the long term[2]. Through the work of Dr. Michael Brownlee we are reaching a deeper understanding exactly how high blood glucose levels cause these complications at the molecular level. Dr. Brownlee's contributions to our understanding of the pathobiology of diabetic complications led the AD to award him its highest honor, the Banting Medal, in 2004. This article reflects what we consider some major learnings from his fascinating Banting Medal address at the 2004 ADA conference.

The first question that Dr. Brownlee addressed is why the retina, kidney and peripheral nerves seem to be selectively affected by the hyperglycemia of diabetes. Dr. Brownlee explained that certain cell types, in particular the capillary endothelial cells of the retina, the mesangial cells of the kidney, and the neurons in the peripheral nerves, cannot adjust to high glucose levels in the blood as well as other cells. Most cell types will shut down glucose transport systems to keep their intracellular glucose levels constant when they are confronted with excess glucose. Certain cells in the retina, kidney, and nerves cannot adapt as easily. While this may explain in part the tissue selectivity of diabetic complications, it does not address what happens inside the cell when intracellular glucose levels go too high. The overarching theme of

[1] For example, Eli Lilly announced in early August the failure of Arxxant for diabetic neuropathy – the drug was in Phase 3 trials and an NDA filing had previously been expected to happen later this year. Lilly has filed for retinopathy, and we will continue to watch progress here.

[2] We already know that the lower the A1c, the better – what we don't know yet is how much reducing variability of blood glucose matters. In other words, how much better is an A1c of 6.5 with a high versus a lower standard deviation, in terms of development of long-term complications?

Brownlee's work is to uncover why cells are damaged by high glucose levels and how we might be able to intervene with pharmaceutical therapies.

In his Banting Address, Dr. Brownlee described a unifying mechanism of diabetic complications. The basis of his hypothesis is that increased production of reactive oxygen species (ROS) in the mitochondria of affected cells may initiate the development of diabetic complications. Mitochondria are specialized cellular structures that produce energy in response to nutrient intake; ROS are by-products of mitochondrial energy production, like exhaust from a car engine. In diabetes, increased glucose concentrations in the cell "rev up" the mitochondrial production of ROS, which can change the cell's metabolism and cause the deleterious complications.

But why should ROS explain diabetic complications? First, the ROS model links four distinct metabolic pathways that are each individually linked to diabetic complications, but are not connected to each other: the polyol pathway, the hexosamine pathway, the protein kinase C pathway, and the advanced glycation end-products (AGE) pathway. A pathway is defined as a set of genes that function coordinately to perform a specific biological function. For instance the glycolysis pathway is a set of ten enzymes whose collective function it is to produce ATP from metabolizing glucose. Individually, each enzyme is not significant, but a collective pathway, these enzymes perform a very important function. All of these pathways are activated by hyperglycemia and are linked with diabetic complications and Dr. Brownlee was the first to show that these four pathways are activated by excess ROS within the cell.

The net effect of increased ROS is that the activity of a key enzyme, glyceraldehyde-3 phosphate dehydrogenase (GAPDH) is decreased. When this enzyme's activity is decreased, metabolites build up within the cell and activate the four deleterious pathways mentioned above. But why is GAPDH activity decreased? Dr. Brownlee's lab found that another enzyme poly(ADP-ribose) polymerase (PARP) mediates this process.[3] PARP normally is part of a pathway that responds to DNA damage that naturally occurs in cells from UV radiation and the natural aging process. Increased ROS formed in the cells of diabetic patients causes DNA damage and thus activates PARP. When trying to fix the damage to the cell's genetic material, PARP recruits GADPH to the nucleus, where it assists in repairing DNA. In effect, PARP steals GAPDH from the cytosol, where it would normally prevent the flux of glucose into the harmful pathways.

Dr. Brownlee highlighted three possible therapeutic targets that stem from his research. The first is the possibility of inhibiting PARP, due to its central role in the causation of diabetic complications. In preliminary studies, PARP inhibitors completely prevented the formation of acellular capillaries, which are a component of diabetic retinopathy. (Dr. Brownlee did not describe any effects of PARP inhibition in other tissues or in human studies.)

The second line of therapeutic strategies involves shunting glucose metabolism away from detrimental pathways. Transketolase is a metabolic enzyme that controls the flow rate of metabolites into the pentose phosphate pathway, which makes, among other things, nucleic acids for DNA and RNA synthesis. Theoretically, the activation of transketolase could force glucose and its metabolites into the pentose phosphate pathway and away from the polyol, hexosamine or AGE pathways that are associated with diabetic complications. Activator drugs, however, are notoriously difficult to make. Fortunately, it is known that thiamine is a required co-factor for transketolase function. Thus, Dr. Brownlee reasons that a thiamine analog, benfotiamine, might also activate transketolase. The administration of benfotiamine to diabetic animals improved their retinopathy.

[3] To avoid any confusion: PARP [poly(ADP-ribose) polymerase] and PPAR [peroxisone proliferators-activated receptor] are very different despite similar abbreviations. Unfortunately, PARP antagonists have not reached the clinical testing stage yet, though this protein remains an attractive drug target.

Lastly, because ROS are at the heart of PARP activation, Brownlee proposed that antioxidants may also be a therapeutic target for diabetic complications. The Brownlee lab treated animals with a dipeptide that mimicked the action of an enzyme antioxidant, superoxide dismutase. Remarkably, this peptide worked as a catalytic antioxidant in the animals, reducing their ROS production substantially.

Clearly, diabetic complications represent a major unmet need today as there appear to be few treatments in late-stage pharmaceutical pipelines. Complications represent the majority of direct costs associated with diabetes – nearly *half* of the $92 billion in direct costs in the US alone, as of early this decade – and patients and HCPs alike remain eager for more effective drugs to address microvascular disease in particular - retinopathy, neuropathy, and nephropathy.

Dr. Brownlee's groundbreaking work has been widely lauded in the diabetes community for its relevance to both basic science and clinical care. The next step forward is to test whether Dr. Brownlee's hypothesis about diabetic complications can be translated into new treatments. While animal data has been convincing thus far, these therapies need to be moved into human trials as quickly and as *safely* as possible. The capacity to treat diabetic complications more effectively would improve both length and quality of life for countless diabetic patients.

*Cullen Taniguchi recently began writing for Diabetes Close Up. He is currently an M.D./Ph.D. student in his fifth year at Harvard Medical School. He is pursuing his Ph.D. in cell biology, which he will complete this year, in the laboratory of Dr. C. Ronald Kahn at the Joslin Diabetes Center. Cullen's research examines the molecular mechanisms of type 2 diabetes, particularly insulin resistance in the liver and how it may be a significant factor in the development of diabetes. Cullen anticipates receiving his M.D. in 2007 and will pursue a career in internal medicine/endocrinology. Cullen was born and raised in Hawaii, attended Occidental College where he was obtained an A.B. in chemistry and then spent two years in Oxford as a Rhodes Scholar studying for a master of philosophy in Economic and Social History. As many readers know, while diabetes is a major cause of morbidity and mortality in the United States, it is even more punctuated in Hawaii, where the many citizens of Asian and Polynesian ancestry are genetically predisposed to diabetes when placed on a western diet.*

### 4. Literature Review - David E. Cummings, M.D. "Gastric Bypass and Nesidioblastosis—Too Much of a Good Thing for Islets?" *NEJM.* 21 July 2005; 353(3): 300-302.

The popularity of bariatric surgery has skyrocketed in recent years, with the number of bariatric operations almost doubling annually. Bariatrics is the fastest-growing subspecialty, the number of bariatric surgeons registered with the American Society for Bariatric Surgery having increased by almost 50% per year in recent years. Bariatric surgery works wonders for type 2 diabetes, appearing to wipe out the disease with the slice of a knife. However, Dr. David E. Cummings makes us question whether bariatric surgery might actually work *too* well.

In this issue of the *New England Journal of Medicine,* Service et al. report that nesidioblastosis, or the "pathologic overgrowth of pancreatic beta cells" that results in life-threatening hyperinsulinemic hypoglycemia, may be a complication of Roux-en-Y gastric bypass. Service et al., experts in the field of hypoglycemia disorders, report that in the past five years, 40% of their nesidioblastosis cases occurred in patients who had undergone Roux-en-Y gastric bypass surgery, while less than 0.1% of the general population has had this surgery. Although researchers have not established a causal relationship between Roux-en-Y gastric bypass and nesidioblastosis, these observations suggest that gastric bypass can lead to pathologic beta-cell overgrowth and hypoglycemia.

Dr. Cummings mentions two of the several mechanisms by which bariatric surgery could result in nesidioblastosis. First, it is possible that in insulin-resistant obese people, adaptive beta-cell hypertrophy develops and causes hypoglycemia after surgically induced weight loss improves insulin sensitivity. Yet several convincing arguments contradict this hypothesis. Service et al. point out that islets are of normal size in obese control subjects without gastric bypass. Also, there is no association between non-surgically induced weight loss and nesidioblastosis or hypoglycemia.

A second possible explanation is more plausible than the first and has far broader implications. This hypothesis posits that Roux-en-Y gastric bypass sometimes results in nesidioblastosis because of long-term stimulation of beta-cell growth and activity by gut hormones that are perturbed by the gastrointestinal surgical procedure. One such gut hormone is glucagon-like peptide 1 (GLP-1), an incretin hormone produced by L cells in the distal intestine. GLP-1 increases insulin secretion and perhaps insulin sensitivity as well. In rodents, the hormone causes beta-cell neogenesis and proliferation, and it inhibits apoptosis. Significant (up to 10-fold) and long-term (up to 20-year) elevations of GLP-1 or other nutrient-stimulated L-cell hormones, such as peptide YY and enteroglucagon, have been seen after Roux-en-Y gastric bypass, biliopancreatic diversion, and jejunoileal bypass surgeries. These operations create shortcuts to the hindgut for ingested nutrients, and since the above-mentioned L-hormones are secreted in response to the passage of nutrients, secretion of the hormones appears to increase in response to these operations. Diabetes in effect disappears within days to weeks after these operations, which is too early for the remission to be explained by weight loss alone. Other mechanisms must play a part, and one possible mechanism is the modulation of gut hormones.

If Roux-en-Y gastric bypass can cause nesidioblastosis by modulating gut hormones such as GLP-1, what does this mean for the promising new lines GLP-1 receptor agonists and dipeptidyl peptidase IV (DPP-IV) inhibitors? Amylin's GLP-1 exenatide was recently approved by the FDA, and Novo Nordisk's liraglutide, Conjuchem's CJC-1131, and Zealand Pharmaceutical's ZP10 are similar compounds in clinical trials. DPP-IV inhibitors increase endogenous GLP-1 by inhibiting DPP-IV, the enzyme that degrades GLP-1. Novo Nordisk's vildagliptin, Merck's sitagliptin, and BMS's saxagliptin are DPP-IV inhibitors currently in advanced clinical trials. If modulation of GLP-1 secretion resulting from bariatric surgery can cause nesidioblastosis, are we playing with fire in looking toward GLP-1 agonists and DPP-IV inhibitors as new therapies?

On the other hand, there is much to say in defense of GLP-1 receptor agonists and DPP-IV inhibitors. First, over a five-year period, the Mayo Clinic hypoglycemia referral center observed only six cases of nesidioblastosis that appeared to be caused by Roux-en-Y gastric bypass. Second, DPP-IV inhibitors do not stimulate GLP-1 signaling as much as high-dose GLP-1 receptor agonists do. DPP-IV inhibitors are therefore probably less likely to cause nesidioblastosis, although at the same time this means that they are less likely to decrease glucose levels as effectively as GLP-1 receptor agonists. Third, doses of GLP-1 receptor agonists that exceed peak endogenous GLP-1 activity are far less effective than Roux-en-Y gastric bypass or biliopancreatic diversion at improving diabetes. This suggests that these bariatric operations increase glucose disposal by mechanisms other just increasing GLP-1. Other gut hormones, such as ghrelin, peptide YY, and oxyntomodulin, may be modulated by bariatric surgery as well. Ghrelin can aggravate diabetes by impairing insulin secretion, stimulating counter-regulatory hormones, and directly opposing insulin action. Ghrelin secretion is reduced following Roux-en-Y gastric bypass. Thus, with so many possible mechanisms through which gastric bypass may increase glucose disposal, the risk of hypoglycemia following gastric bypass should be higher than the risk caused by medicines that selectively increase GLP-1 signaling.

In his conclusion, Dr. Cummings writes " *…Nesidioblastosis probably represents the pathologic extreme of a phenomenon that would benefit the vast majority of obese patients with diabetes*." Moreover, great

benefits may be gained from the finding of gastric bypass-induced nesidioblastosis. The link between gastric bypass surgery and nesidioblastosis should be explored. If the surgery stimulates beta-cell-trophic factors, research should be conducted to identify these factors so that they can be used to treat diabetes.

*--by Katelyn Gamson*

**5. Like Chocolate for Medicine**

The mention of chocolate often elicits strong positive reactions among connoisseurs of its luscious taste and versatility as an ingredient. For those who need higher justification, the serotonin boost suffices. Now, research indicates that chemical components of its active ingredient could be helpful in managing the macrovascular complications associated with long-term diabetes." Chocolate has lately been hailed for its large amounts of phytochemicals, potentially health-promoting naturally occurring compounds in plant foods such as garlic, tomatoes, and cocoa. A class of phytochemicals called flavanols, a subgroup of flavonoids, are abundantly present in chocolate. Flavanols have the potential to treat strokes, diabetes, and vascular dementia.

More than 30 articles were retrieved by PubMed when we searched for "chocolate flavanols." Article titles in the results list ranged from "Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans" (Fisher, Hughes) to "Short-term administration of dark chocolate is followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy persons" (Grassi, Lippi). Flavanols can expand the synthesis of nitric oxide in the blood, which in turn increases blood flow and can aid in the treatment of vascular complications that accompany long-term diabetes. They have also shown therapeutic effects similar to aspirin in reducing platelet aggregation. Their ability to increase blood flow to the brain may make them useful in the treatment of vascular degeneration caused by stroke.

Mars, Inc. has supported research on cocoa for the past 15 years. In a meeting hosted by Mars earlier this year (appropriately held in Switzerland!) scientists convened to discuss their independent research on cocoa flavanols in a peer-review setting. Scientists at Mars have discovered that "libraries" of cocoa flavanols can be synthesized and that new flavanols can be generated from natural flavanols, increasing their attractiveness for use in pharmaceutical drugs. Researchers who have worked extensively to understand the properties of flavanols are now going on the record to express enthusiasm and optimism for their possible pharmaceutical use. "Many scientists believe there are multiple restorative qualities, and they are racing to prove their theses. Flavonoids are only the beginning," says Bruce R. Gilardi, CEO of up-and-coming Savoia Chocolate in New York City.

Someday, patients may receive prescriptions for flavanol pharmaceuticals. Until then, however, directions to the local chocolatier will not be substituted. First, the obvious contraindication remains: chocolate tends to be high in fat and sugar, both of which are generally unhelpful in the management of type 2 diabetes. Second, it may turn out that the concentration of flavanols in processed chocolate is less than sufficient for optimal therapeutic effect. But we live in hope that the pills will taste like chocolate….

*--by Nupur Lala*

**6. Second Quarter Patents and Applications for Glucose Monitoring (April through June 2005)**

A search of US, European, and World patents and applications relevant to glucose monitoring (using proprietary search strategies) yielded more than 170 citations for April, May, and June 2005. The citations are shown in Table 1. These citations were sorted into three categories; those using (1) noninvasive or minimally invasive techniques (N/M), (2) subcutaneous implants for continuous monitoring (S/C), and (3) blood or other bodily fluids, such as interstitial fluids (B/F). The results showed that approximately

55% were in the B/F category, about 25% was found in the N/M category, and about 20% were found in the S/C category.

We have selected several interesting patents from this period and have summarized them below and on our website. Note that published claims in an application could undergo significant changes before they issue in a patent.

In an application assigned to Microchips, Inc. (WO05041767A2: MEDICAL DEVICE FOR SENSING GLUCOSE) a multi-use glucose sensor is described. Specifically, medical devices, utilizing multiple reservoirs to protect and selectively expose sensors or other reservoir contents, are provided having (i) a reservoir contents destruction mechanism to interrupt the release or exposure of reservoir contents, for example, to deactivate an unneeded sensor and prevent it from negatively impacting other sensors, (ii) a protective covering material layer over the sensor underneath the reservoir cap, which protects the sensor membrane and sensor during reservoir cap disintegration and then is removed, (iii) a device design for containing sensors in shallow, wide reservoir structures to enhance sensor exposure by minimizing molecular diffusion distances, (iv) an implantable sensor unit and a separate drug delivery unit, or (v) combinations thereof.

*Claim 1. A device for the controlled exposure of a secondary device, comprising: a substrate; a plurality of reservoirs in the substrate; an operational secondary device in one or more of the reservoirs; a reservoir cap covering each of the reservoirs to isolate the secondary device from an environmental component outside the reservoirs, wherein the reservoir cap is impermeable to the environmental component, means for disintegrating or permeabilizing the reservoir cap to expose the secondary device to the environmental component, and means for selectively rendering the secondary device inoperable.*

In the field of continuous monitoring, particularly using implanted sensors, sensor-drift is a serious problem. Published US Patent Application (US20050143635A1: CALIBRATION TECHNIQUES FOR A CONTINUOUS ANALYTE SENSOR; unassigned, but the related PCT application has been assigned to DexCom, Inc.) describes systems and methods for overcoming this problem. For example, in the case of a continuous glucose monitor, the inventors describe the use of a physiologically invariant non-glucose signal analyte, where a sensitivity change associated with the solute transport through the membrane system is measured. Such measurements may provide a baseline or sensitivity measurement for use in calibrating the sensor. Furthermore, baseline, and/or sensitivity measurements may be used to trigger events such as digital filtering of data or suspending display of data.

*Claim 1: A method for measuring a sensitivity change of a glucose sensor implanted in a host over a time period, the method comprising:*

- *measuring a first signal in the host by obtaining at least one glucose-related sensor data point, wherein the first signal is measured at a glucose-measuring electrode disposed beneath an enzymatic portion of a membrane system on the sensor; and*
- *measuring a second signal in the host by obtaining at least one non-glucose constant data point, wherein the second signal is measured beneath the membrane system on the sensor; and*
- *monitoring the second signal over a time period, whereby a sensitivity change associated with solute transport through the membrane system is measured.*

A patent to be noted as much for its claims as for the term of the patent, US6887426: REAGENTS TEST STRIP ADAPTED FOR RECEIVING AN UNMEASURED SAMPLE WHILE IN USE IN AN APPARATUS, appears to be a Lemelsonesque patent (Jerome Lemelson, the inventor who gave notoriety to "submarine patents"—patent applications that the inventor had manipulated to issue as late as

possible, but which claim advantage to a very early priority date; a practice squashed by the patent act of 1995) that claims priority to a August 13, 1986 filing but was filed on June 24, 2002 and issued on May 3, 2005. Assuming that the priority claim can be confirmed, this patent will expire on August 13, 2006. A rather short life for a patent that was issued only on *May 3, 2005*! More interestingly, a related patent application that was filed earlier and issued earlier than the 6,887,426 patent—the 5,563,042 patent that was filed Mar. 21, 1995, and issued on Oct. 8, 1996, will expire only on *April 9, 2011*! Despite the short lifespan of the 6,887,426 patent, the assignee, Lifescan (J&J), has plenty of other related patents (126 of them!) to protect their strip franchise.

*Claim 1. A regent test strip for use in an apparatus for determining a blood glucose concentration of a sample of whole blood, the apparatus including optical means for detecting intensity of light reflected from a reading surface portion of the reagent test strip, the reagent test strip comprising:*

*a reagent pad including:*

- *a sample receiving surface portion for receiving an unmeasured whole blood sample;*
- *a reading surface portion, other than the sample receiving surface portion, from which reflectance is read by the apparatus; and*

*a rigid handle to which the reagent pad is attached, wherein the rigid handle is configured to provide access to the sample receiving portion by the sample and access to the reading surface by incident light from the optical means such that the reagent test strip is adapted for receiving the unmeasured whole blood sample while in use in the apparatus.* We have included this quarter's table on our website – please see our reports area to download the page at www.diabetescloseup.com.

*This list and review were produced by Russ Potts, Ph.D. of Russ Potts Consulting, LLC (russ@vosspotts.org) and D. Bommi Bommannan, PhD, JD of MaxVal Group, Inc (bommi@maxvalgroup.com).*

**7. Conference Preview**

- **AADE**, Washington, DC - August 10–14: The AADE just began and we are in Washington DC now – if you are here and would like to see our top picks, you can download our schedule gratis at www.diabetescloseup.com (under reports). This year, there are more than 7,000 people in attendance and we tip our collective hat to the AADE for bringing us some terrific sessions, including
    - Alan M. Spiegel, MD on NIH Support of Research and Education on Diabetes
    - Gary Scheiner, MS, CDE on Setting and Fine-Tuning Pump Basal Rates
    - Nugget Burkhart, MA, CDE, The Child With Type 1 Diabetes – Past, Present, Future
    - Anne Peters, MD, Conquering Unique Challenges in Diabetes Management
    - Francine Kaufman, MD/Paula Jameson, MSN, CDE, Current Research and Management of Children with Type 2 Diabetes
    - Julie Koppert, RN, CDE, Joan Thompson, PhD, CDE, Diabetes Prevention: How it Works in the Primary Care Setting

  The social events supported by Bayer, Novo Nordisk, and Lifescan have been offering us some great opportunities to meet so many terrific CDEs as well as people in the industry. After days one and two – we're loving it! We'll have a full report in the fall, and until then, check out our daily blog reports on www.closeconcerns.com.
- **EASD** is in Athens in just a few weeks - September 9–15. We understand that for this meeting, EASD received 2313 abstracts for review, a record number, up 15% from last year. To boot, US and Asian submissions have risen 25%. The full program is available for downloading (PDF) from the EASD website www.easd.org and our schedule will be up on our site shortly. Key sessions at EASD will include the release of the PROactive trial results and full data from the

Medtronic GuardControl trial – sounds like there will also be peds data at ISPAD, which is in Poland in late August/early September.

- **North American Association for the Study of Obesity - www.naaso.org** meets in Vancouver, British Columbia, October 15–19.
- **The Diabetes Technology Society** meeting takes place in our fair city by the bay (www.diabetestechnology.org) November 10–12. Ross Jaffe, MD, of Versant Ventures and Kelly L. Close are co-organizing a morning on the "Business of Diabetes" – what should be some terrific discussions on glucose monitoring, insulin delivery, pharma, and stem cells – more to follow! We hope to see you there ~'til then, have an excellent end of summer!

*Diabetes Close Up* is a newsletter highlighting notable information and events related to selected companies with the diabetes industry. This newsletter is put forth as an unbiased commentary on the industry. If you have any suggestions or comments regarding content, please contact info@closeconcerns.com. If you would like to 1) unsubscribe; 2) add a name to the DCU mailing list; or 3) offer any suggestions or comments regarding content, please write to info@closeconcerns.com.

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