DIABETES CLOSE UP

Diabetes Close Up
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Breathless ~

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

From the Editor:

There's been so much happening in diabetes that every _day_ we think of publishing the newsletter, more happens – it's crazy. Conferences (never-ending, but so exciting), metabolic syndrome controversy (is it real? is it not?), cardiologists taking over endocrinology, oh-so-telling NEJM *and* JAMA *articles and editorials, ADA vs AHA, panel complaints, new FDA requirements, failed partnerships, the death of the dual PPAR, delays on inhaled insulin, new CDC stats – we can barely look up! We've been publishing more and more on our blog and our list inside shows what you can catch up on there, in addition to this newsletter.*

We update you in this issue on the most recent set of conferences, NAASO (obesity – and what a meeting this year!) and the Canadian Diabetes Meeting; additionally, we offer an interview with diabetes expert Dr. Paul Zimmet (we could've talked to him for a million hours), give you our current take on Novo, set you up for the Diabetes Technology conference and AHA (oh, you thought it was a cardiology meeting? Why?), recount this month's JAMA *early release on Pargluva (brilliant), and go a bit around the edges of diabetes, closing with our own take on metabolic syndrome and an interview of note on bariatric surgery.*

Because we know you like us but you start to cry when we exceed 30 pages, we've decided to save our extended commentary on AADE and EASD for a volume we're now calling Diabetes 2006. We've been wanting to make this available for a couple of months – it's our take on meetings and conferences and important goings-on in diabetes over the last year along with our models and a look ahead. Same problem here, every time we were ready to publish, there was another meeting upcoming that we wanted to fit in! We've now decided to wait until the last three key meetings of the year – the Diabetes Technology Meeting, AHA, and the Levine Symposium – are finished, and then we'll wrap it up! We've included 30-plus pages each on the most key sessions and takes on EASD and AADE in this volume, along with our favorite piece so far, what the new products are all _really_ like – based on front-line investigation into and use of disposable pumps, Symlin, and continuous monitoring.

–by Kelly L. Close

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

1. **Blogwatch - See below for blogs since our last newsletter – you can see any update online at http://www.closeconcerns.com/ -**
   - **October 28, 2005: BMS Negativity on Pargluva Re-affirmed/Inhaled Decision Put Off 90 Days**
   - **October 27, 2005: BMS Issues Statement Re: Pargluva**
   - **October 27, 2005: New CDC Stats - 20.8 mm Americans with Diabetes, Up Significantly**
   - **October 27, 2005: Novo 3Q05 Results**
   - **October 26: 2005: Amylin Reports 3Q05 – Excellent!**
   - **October 26, 2005: NAASO – Posters – AC137**
   - **October 20, 2005: Canadian Diabetes Association Meeting in Full-Swing**
   - **October 19, 2005: ABT Reports 3Q05**
   - **October 18, 2005: J&J Reports 3Q05**
   - **October 18, 2005: FDA Says Hold On to Pargluva!**
   - **October 18, 2005: NAASO – Day Three Postscript – Exhibit Action**
   - **October 18, 2005: NAASO, Day Three – Economics and Such**
   - **October 17, 2005: NAASO, Day Two – Framingham and Kids**
   - **October 16, 2005: NAASO, The Obesity Society, Day One**
   - **October 14, 2005: Kaiser - 'Take the Long Way 'Round'…Is That the Best?!**
   - **October 13, 2005: Bariatric Surgeries and Reimbursement—Worth the Investment?**
   - **October 11, 2005: Medtronic Analyst Day – Diabetes Takes the Cake!**
   - **October 11, 2005: Kidney Failure Rate Stabilizes**
   - **October 7, 2005: Friday Stream of Consciousness on Ranbaxy-Lantus-Apidra-Symlin-Pumps**
   - **October 5, 2005: Novo Expanding Sales Force by 400 Reps According to our Intelligence**
   - **October 5, 2005: In-Store Clinics at Major Pharmacy Chains May Boost Sales**
   - **October 4, 2005: Dr. Richard Nesto – Excellent Conference Call!**
   - **October 3, 2005: CCS Medical and MP Totalcare Power Merge through Warburg**
   - **September 30, 2005: Conjuchem – Yet Another Miss, Abandoning GLP-1 Daily Product**
   - **September 29, 2005: Novo (Novo!) Downgraded Due to LAR Strength**
   - **September 28, 2005: Diabetes Care and Kids – 8.5 and Stuck!**
   - **September 20, 2005: Byetta Update – wow!**
   - **September 20, 2005: Novartis Pipeline Update – LAF237 Fails to Show Non-Inferiority to Metformin**
   - **September 14, 2005: EASD Day Four – Posters!**
   - **September 13, 2005: EASD Day Three – GuardControl!**
   - **September 12, 2005: EASD Day Two – PROactive! – Hypoglycemia**
   - **September 11, 2005: EASD Day One – PROactive, GuardControl, Abbott's Navigator, and Rimonabant**

2. **Paul Zimmet on Diabetes Today**

Kelly was in Melbourne, Australia recently, where she was lucky enough to sit down with the great Professor Paul Zimmet, *Foundation Director of the International Diabetes Institute there. Dr. Zimmet is perhaps most well known for his insights into genetic and lifestyle influences on type 2 diabetes and for his research on the epidemiology of diabetes, although recently he has received substantial attention for his work on pre-diabetes, having co-organized the First International Congress on Pre-Diabetes in Berlin earlier this year. See the August DCU for our review on this superb meeting. Professor Zimmet has received many awards, including the ADA's Kelly West Medal, the Eli Lilly Award of the IDF, the EASD's AM Cohen Award and the Diabetes UK Banting Award Lecture. He has published over 550 scientific papers, chapters and reviews in peer-reviewed journals and books on various aspects of diabetes research and is co-editor of* The Epidemiology of Diabetes. *Of course, I was thrilled to have the chance to talk at length with Professor Zimmet and to ask his opinions on everything ("evera-thing" as they say in Australia – and it's so nice, everyone calls you "love"!) going on in the field of diabetes. The following represents Dr. Zimmet's significant candor, fascinating perspective, and overall take on a wide range of topics related to diabetes goings-on:*

On defining metabolic syndrome: There's been a lot of confusion because of several different definitions. The first one actually was in 1999, and then there was the WHO one, for which I co-chaired the committee with

Professor Alberti.[1] It was just a first attempt to define the syndrome. In fact, it was *not* very useful clinically—it was far too academic, and the ATP3 definition by the American Heart Association actually was much more useful from a clinical point of view. But some of the criteria, particularly those for obesity, were not really in line with other European populations, and certainly were not relevant to populations in Asia. So the IDF decided to look at coming up with a new definition that would be useful firstly for primary care physicians and health care professionals to spot people who are at the highest risk of diabetes and cardiovascular disease, and secondly for its relevance to other populations, particularly those in Asia and other ethnic groups. The new definition highlights central obesity as an essential feature; in order to have the metabolic syndrome, you have to have central obesity based on waist circumference, which is very simple to measure in the consulting room. Diagnosis of the metabolic syndrome also requires two other criteria: one of low HDL cholesterol, raised triglycerides, hypertension, or some form of glucose intolerance, be it diabetes or pre-diabetes. (DCU note – the new definition to which Dr. Zimmet refers emerged at the First International Congress on Pre-Diabetes and the Metabolic Syndrome, held last April in Berlin. We'll be including a full review of this meeting in our upcoming compendium of conference reviews – for more information now, see our view of the meeting highlights in our August, 2005 *Diabetes Close Up*, available on our website. Generally, the new definition focuses heavily on central obesity and insulin resistance as critical causative factors.[2])

On the term pre-diabetes: The term pre-diabetes is controversial because it is a term that was coined by the ADA mostly for public relations. And it's quite reasonable for the lay public, since it is easier to talk to the public about pre-diabetes than it is to talk about impaired glucose tolerance or impaired fasting glycemia. Pre-diabetes basically covers the terms of impaired glucose tolerance and impaired fasting glycemia. Now, that in itself is an issue because the ADA definition of impaired fasting glycemia is set at a plasma glucose level of 100 mg/dl, whereas the WHO definition is set at around 120 mg/dl. There is a need for these to be brought closer together. … Do I think it will happen, you ask? Well, I wish I could say that it will happen, and I do hope it will. I'm certainly in favor of the WHO coming in line with the ADA, and our own epidemiological data in a number of populations confirmed that the ADA decision is the correct one. But whether the WHO will take that line, I don't know. I understand there will be an expert committee very soon for WHO to reexamine its position.

On prospects for drug approval for the metabolic syndrome: I guess one of the problems is lack of a definition of the metabolic syndrome and knowledge about its outcomes. We now know that people with the metabolic syndrome are at two times the risk of getting a heart attack or stroke, and five to six times the risk of type 2 diabetes. So I think there is an increasing feeling that if you diagnose the metabolic syndrome, it should be treated. And of course, in treating it, you might need anything up to four or five different drugs. So the ideal situation is to come up with a polypill. At the moment, you could actually say that rimonabant is a potential in that area. The glitazone drugs and PTP1B inhibitors are also potential metabolic syndrome drugs. (*DCU note - PTP1B is an enzyme that basically inactivates insulin – see below for more on this*.) So I think at the moment although there is a lot of resistance from drug agencies like the FDA, this is a *real* condition, and it is associated with serious morbidity and mortality. At some stage they are going to have to strictly address the issue of registering drugs for treatment. When that happens is anyone guess, but for me, it should be sooner, not later.

On diet and exercise versus drugs: The whole issue of prevention is clearly complicated. While it is clear that you can reduce new cases by over 50%, the two major studies that demonstrate this were studies that had very intensive support for the people concerned—dieticians, exercise physiologists…. So I think it is very good from a scientific basis for us to know that these different strategies will work, and a number of individuals will have the

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[1] Like Dr. Zimmet, Sir George Alberti is a very well known international figure in diabetes. He is the immediate past President of the Royal College of Physicians in London, and works closely with both the International Diabetes Federation and the World Health Organization. He has published more than 1000 articles on diabetes and metabolism.

[2] As the DCU August #51 'On Pre-Diabetes' notes, according to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:

- Central obesity (defined as waist circumference ≥ 94cm for European men and ≥ 80cm for European women, with ethnicity specific values for other groups – for now, the US is sticking to 102 cm for men and 88 cm for women) plus any two of the following four factors:
- Raised TG level: ≥ 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality
- Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

rigor to follow those patterns. But in the majority of cases there would need to be major changes in community infrastructure. I mean, you can't go to a low-income group with a high prevalence of diabetes and tell them to exercise or lose weight when the correct food may not be there, or there aren't exercise facilities or gymnasia around. So there is a real world, and in that situation, drugs are certainly a possibility, and it is quite clear to me that metformin, acarbose, and TZDs do in fact aid in reducing progression to type 2 diabetes. It is also quite possible that drugs perform *better* than diet and exercise; for example, there is a study in China that showed that people who received metformin or acarbose actually did better in terms of prevention than people on lifestyle modification. So the jury's still out, isn't it? Obviously, it is our responsibility to recommend lifestyle change *first* rather than pharmacotherapy.

On rimonabant: Rimonabant is a very exciting new drug. There is no question about its very positive effects in reducing a number of the risk factors of the metabolic syndrome, besides obesity. There is reduction in lipids, improvement in insulin sensitivity, lowering of glucose, and some effect on blood pressure. And of course, it is effective in reducing smoking, although this isn't often quoted. Now, there is some concern that the side effects from the CNS side might actually cause some problems when it is more widely available but this has not been a problem in the clinical trials. These are clinical trials, and I guess one will have to see when rimonabant comes out into the wider community whether its side effects are in fact a bigger problem than would appear from the relatively positive clinical trials.

On PTP1B inhibitors: The PTP1B area is very interesting. PTP1B inhibitors improve insulin sensitivity and also appear to have a very positive effect, like rimonabant, on obesity and other risk factors for cardiovascular disease in animal studies. We know that if you inhibit the enzyme, insulin will hang around longer, and this will improve insulin action. I am particularly interested in this area because I chair the SAB (scientific advisory board) of a biotech company in Connecticut called The Institute for Diabetes Discovery that has an excellent candidate now licensed to a new pharmaceutical group, Alinea. (DCU note – we love when everything dovetails – see elsewhere in this issue for commentary on recent funding of Alinea, what looks to be a most promising new biopharmaceutical company focused on development of new therapeutics for diabetes and other metabolic disorders based in Cambridge, MA.) Eli Lilly was working with a group that had developed a compound which I understand has not gone further and I believe there may be one or two other companies in the field. The IDD compound has been through animal studies and it looks like they are going into human studies in the not too distant future. They probably have the best prospect of a drug in that area and there has been quite a bit of interest in the pharmaceutical industry.

On different pathways for obesity: At the moment everyone is excited about endocannabinoid receptor blocking, which is the rimonabant pathway, as you know. There are a lot of pathways, and as I noted, the PTP1B inhibitor group looks very promising for obesity as well as diabetes. So to put it simply, there are a number of pathways, and no *one* drug will cause people to lose 20 or 30 kilograms. It's most likely that combinations of drugs working through different pathways, just like in diabetes to a certain extent, will have a cumulative effect and get people to lose more weight than one drug alone would.

On ISF402: I can't say much about that, because I discovered it.

[Interjection] *I know, but it's really exciting….*

Well, as a result of my Ph.D. 30 years ago, I discovered a substance in the urine that lowered blood sugars in laboratory animals. It took until four or five years ago for my colleague, Professor Frank Ng, who was my Ph.D. supervisor, to finally purify the extract enough to sequence the compound. We discovered that we had a very small molecule—four amino acids and that is very stable and works orally in laboratory animals to reduce blood glucose. That particular molecule is now undergoing toxicology studies in laboratory animals. If they are successful, it could go to the first human trials the middle of next year. It's a very early stage of development, but it's quite exciting.

On the Selenoprotein: This is a protein we discovered in the pancreas which appears to protect the pancreas against stress. You know, in type 2 diabetes, of course, you have overweight people with a lot of pressure on the pancreas. So you get oxidative stress. This then triggers an inflammatory response that can cause further beta cell damage. This protein is in the same area of the pancreas as insulin. It may be very protective. We published the original paper in *Diabetes* and it was called Tanis two years ago, but it's now called SelS—it's a Selenoprotein. The

property is owned by an exciting Australian biotech company, Chemgenex (www.chemgenex.com) that was listed on the NASDAQ in late June (2005). It was an Australian group working with a number of international pharmas to develop new drugs for diabetes, but recently took over a company in Menlo Park; the company is focused on cancer, diabetes, obesity, and depression.

On bariatric surgery as an alternative to drugs: Well, you know, one of the leading groups in the world in obesity surgery is actually right here in Melbourne. A couple of years ago, John Dixon and Paul O'Brien published a paper in *Diabetes Care* showing that people with type 2 diabetes who had the surgery lost their diabetes. (DCU note – the landmark paper, *Health Outcomes of Severely Obese Type 2 Diabetic Subjects 1 Year After Laparoscopic Adjustable Gastric Banding*, was published in the February 2002 *Diabetes Care* and showed that of 50 patients studied, remission of diabetes occurred in 32 (64%) and major improvements in glucose control occurred in 13 (26%) – glucose metabolism was unchanged in only 5 (10%).) …And there were earlier procedures before gastric banding. It has been well demonstrated that if you operate on people with impaired glucose tolerance and they lose weight, they don't get diabetes. So if you have very good criteria for whom you operate on—people with type 2 diabetes who are morbidly obese and can't lose weight by other means—there is *no question* that it works. The only issue is that you don't go and do it on someone who is moderately obese, who could lose weight by lifestyle measures if they persisted.

Of course, you know, there can be side effects from the surgery. It's terrific to lose your diabetes, but there is quite a high rate of complications, or people who just are not feeling well. They've got a small stomach, they've got to eat small amounts...

On, overall, progress in the field of diabetes: At the ADA in Orlando (DCU note – 2004), Mark Atkinson gave a lecture on why, after 30 years of research, we still do not know what causes type 1 diabetes. That is the biggest disappointment for me. After all these years no one *really* understands what causes type 1 diabetes, although we *think* we do. Basically it has been a dead end to research, and I wrote an editorial in *Lancet* last year[3] saying I think we need new people in the area, filled with new ideas—lateral thinkers. Since we don't understand what causes type 1 diabetes, it is very hard to start trying to prevent it. Everything is a 'blunder bus' approach, you know, try this drug, try that drug. There is too much copycat research. They see that something causes type 1 diabetes, 50 people jump in on it, and it's a dead end. And it caused the disappointment that after 30 or 40 years since people started doing transplantation, we still have not got it right.

I think another one of the problems in diabetes is that nearly all the work in diabetes is being done in rats and mice. That is all we've got to work on, and discoveries in mice and rats are not necessarily relevant in humans.

[Interjection] *Is that because the immune systems are very different?*

Well, the genetics and immune systems could be quite different. We are very happy with the Israeli sand rat because it is actually a gerbil, and we have evidence that any of the genes related to obesity or diabetes that we've discovered in this animal have up to 90% similarity to human genes.

I guess the thing I am most pleased about is the progress that has been made in reducing the risk of complications. In type 1 diabetes 20 years ago, people were getting all sorts of complications—eye problems, kidney disease, and neuropathy. With much better therapies, self-monitoring and better insulins and diabetes education, the chances of complications have been substantially reduced. So I think that is a big win for research. We still don't know what genes cause type 2 diabetes or what causes type 1 diabetes, but at least research has brought us better prospects for people with diabetes, both type 1 and type 2. So we've got to pat research on the back, but we still have not delivered in the big picture.

On the biggest-picture thoughts from Berlin: I think a major issue, which people in government may not yet be prepared to face because of the cost, is that you can potentially prevent type 2 diabetes by treating people with IGT using certain drugs. And not only can you reduce diabetes, but you can substantially reduce the cardiovascular disease burden. I think in the next five or ten years we are going to be treating pre-diabetes much more actively.

[3]The Lancet 2004; 364:1645-1647 *The rising tide of childhood type 1 diabetes—what is the elusive environmental trigger?*

Thanks so much to Dr. Zimmet for his generosity in spending time with us! We look very forward to the Second International Congress on Pre-Diabetes, scheduled for March 25-28, 2007 in Barcelona. (http://www.kenes.com/prediabetes2007/).

--by Kelly L. Close

This is the third in a series of interviews of note to be published by DCU – our first was published in April, a discussion with John Eng, powerhouse inventor of exenatide – now known as Amylin's Byetta. That interview can be found here http://www.closeconcerns.com/dcu/47%20Diabetes%20Close%20Up.pdf. The second was a chat published in September with Bob Knorr on reimbursement and the Medicare Modernization Act and it can be found at http://www.closeconcerns.com/dcu/DCU_September_2005_51_FDA_MMA_EASD.pdf. If you have suggestions for future interviews, please write Kelly at kclose@closeconcerns.com. Thanks very much!

3. Metabolic *What*? – a Review and the DCU take

The metabolic syndrome has been a hot topic over the past few months and is an especially important subject due to the size of the population it potentially involves—approaching 50 million people in the U.S. alone. Since about 80% of our conversations about this topic start, '*yeah, so what is going on with that again*?', we thought we'd provide some background for a start. The "battle," as the *JAMA* piece on this topic "Does the Metabolic Syndrome Really Exist?" calls it, began in late August when the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), two of the largest diabetes organizations worldwide, published a joint statement on the metabolic syndrome in *Diabetes Care* and *Diabetologia*. In their statement, the ADA and EASD took the first shot, concluding that the criteria of the metabolic syndrome are ambiguous or incomplete and questioning the clinical value of the diagnosis in the first place. Sheesh! We were very surprised about this – obesity is such a problem, type 2 diabetes continues to grow, treatments aren't working … why de-emphasize problems? Here, we try to unravel the controversy.

In a Nutshell

The disagreement over the metabolic syndrome controversy really comprises two distinct debates. First, does metabolic syndrome exist? And amongst those who believe in metabolic syndrome, the question becomes, what is it? Both of these debates seem to turn on a few key questions:

As to its validity:

1 – Are these factors somehow synergistic, and is therefore the CVD risk of the cluster of factors higher than the additive risk of the individual factors?

2 – Is there clinical value in making a diagnosis? Critics note that the treatment plan is not different than would be for the individual factors.

And as to its definition:

3 –What is the underlying pathology of all these co-morbidities? The WHO definition, for instance, is predicated on the belief that insulin resistance is the root cause of the constellation of problems. The NCEP and IDF definitions focus instead on environmental factors as the cause, and still others believe that inflammation is driving metabolic syndrome.

4 – If metabolic syndrome does indeed exist, what should be included as criteria for diagnosis? The NCEP/ATP definition includes two lipid criteria (HDL and TG) out of five (three total required for diagnosis), whereas the WHO definition requires insulin resistance and combines HDL and TG into one criterion out of four (two plus insulin resistance required for diagnosis).

While evidence exists on both sides of the debate, we strongly believe there is value in the diagnosis as a wake-up call and a fast track to early treatment.

The Makings of a Controversy

The authors of the ADA/EASD piece point out several weaknesses of the metabolic syndrome definition and question whether it is even a syndrome at all. Richard Kahn, the Chief Scientific and Medical Officer of the ADA and one of the authors of the ADA/EASD paper, commented that the combination of CVD risk factors in the

metabolic syndrome may *not* add up to a higher cardiovascular risk than the individual components, thereby failing to really earn the title of "syndrome." Other critiques from Kahn and his co-authors include:

- The criteria of the metabolic syndrome are ambiguous or incomplete;
- The value of including diabetes in the definition is uncertain;
- Insulin resistance as the unifying pathophysiological process is questionable;
- CVD risk factors were included/excluded from the definition arbitrarily;
- CVD risk is variable and depends on which specific risk factors are present;
- The CVD risk associated with the metabolic syndrome does not appear to be greater than the risk due to the sum of its parts;
- Treatment of the metabolic syndrome does not differ from treatment of each of its components; and
- The medical value of diagnosing the metabolic syndrome is questionable.

So what do the other guys say? Wellllll, on the *other* side of the debate, as you might imagine, are the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI), who published their own statement on the metabolic syndrome in mid-September. In it, they refined their definition of the metabolic syndrome and affirmed their belief that the syndrome is a real, growing health problem. Who can argue with this! We feel like these guys are gaining momentum without even trying. Dr. Robert Eckel, president of the AHA and a member of the AHA/NHLBI writing group, acknowledged that the definition of the metabolic syndrome is imperfect but affirmed that the syndrome is relevant for emphasizing the important role of lifestyle changes in reducing risk factors for diabetes and cardiovascular disease (CVD).

According to the AHA and NHLBI criteria, a person has the metabolic syndrome if at least three of the following five conditions are met:

- Waist circumference ≥102 cm (40 in) in men and ≥88 cm (35 in) in women.
- Triglycerides level ≥ 150 mg/dl or the person is receiving drug treatment for elevated triglycerides level.
- HDL cholesterol level <40 mg/dL in men and <50 mg/dL in women, or person is receiving drug therapy for reduced HDL cholesterol level.
- Blood pressure ≥130 mm Hg (systolic) or ≥85 mm Hg (diastolic), or person is receiving drug treatment for hypertension.
- Fasting glucose level ≥100 mg/dL, or person is receiving drug treatment for elevated glucose level.

As noted in the original metabolic syndrome criteria, published in a guideline by the National Cholesterol Education Program Adult Treatment Panel III (ATP III) in 2001, an estimated 47 million individuals in the United States have the metabolic syndrome. That's a big number. According to the ATP III criteria, persons with the metabolic syndrome have about *twice* the risk of developing atherosclerotic CVD compared to those without the syndrome, and about *five times* the risk of developing diabetes. Generally, we feel it can't be a bad idea for people to receive official early warnings on this front.

An Early Wake-Up Call

According to the commentary in JAMA, advocates of diagnosing the metabolic syndrome assert that diagnosing the syndrome is useful in getting people to address their emerging risk factors before they develop diabetes or CVD. Again – hard to disagree with that from our view. Scott M. Grundy, MD, PhD, chair of the AHA/BHLBI writing group, commended the value of the metabolic syndrome diagnosis because treatment of the syndrome normally starts with lifestyle modifications such as exercise, diet improvement, and weight reduction. Treating the individual risk factors of the syndrome as they develop, on the other hand, drives a drug approach for treatment rather than a lifestyle modification approach, according to Grundy. While we basically don't think lifestyle modifications work for most, we like the idea of getting people started *thinking* about it earlier. Okay, heck – yes, *worrying* about it earlier! It's not that we think leading by fear is actually a good idea but … anything to prompt a responsible response.

The ever-present implication of these debates, of course, is labeling for new drugs. If metabolic syndrome exists, then a drug could receive a label for it, and the broader the label (anything for metabolic syndrome is the definition of broad), of course, the broader the demand. We understand that it is smart for the FDA to be very cautious about metabolic syndrome approvals, but we are a long way from this! That said, we also do think there would be value in

such a therapy, if one could be developed – while yes, people can just take different drugs for their many different ailments (glycemic, lipid, and BP), we also know adherence to medication (a nicer way of saying compliance) is something that keeps managed care awake at night. And so it should, with so few patients with diabetes reaching glycemic (to say nothing of other) targets. At last look, the percentage of patients with diabetes meeting glycemic, blood pressure, and lipid targets was only a tenth of the entire group.[4] Only a *tenth*!

Additional Perspectives: ACE and AACE

We point out that the JAMA piece doesn't bring in the position of two other important associations – the American College of Endocrinology (ACE) and American Association of Clinical Endocrinologists (AACE). This is not surprising, since ACE/AACE seems to get very little visibility - far less than they deserve, in our view – everything they do is *so* well done, but it just doesn't seem to get press like the ADA does, unfortunately. We loved their response to the recent concerns and questions about the metabolic syndrome, which was to put out a position statement on October 14, saying that this is an important syndrome (basically agreeing with AHA) and that their opinion hasn't changed since they put together their position paper in 2003. According to the associations, their reason for publishing a position statement was out of concern that recent statements on the metabolic syndrome published by medical organizations would "create uncertainty and controversy among physicians and further confuse the general public." In this position statement, entitled "Reaffirmation of the 2003 ACE Insulin Resistance Syndrome (IRS) Position Statement," ACE and AACE stand by their original 2003 position statement in which insulin resistance syndrome is used to describe the cluster of clinical features that tend to occur in insulin resistant/hyperinsulinemic individuals. According to AACE President Dr. Bill Law Jr., the IRS concept was created to help health care professionals predict and prevent complications from conditions such as CVD and diabetes. People with insulin resistance have an increased risk of diabetes, CVD, polycystic ovarian syndrome, fatty liver, and certain cancers, and IRS diagnosis could potentially make physicians more aware of a patient's risk for any of these diseases. So as a shortcut, we can assume that ACE/AACE agrees more with AHA than with ADA/EASD. This position statement, by the way, can be seen at http://www.aace.com/clin/guidelines/ACEIRSPositionStatement.pdf and is the best thing we know to read about metabolic syndrome.

The Evolution of Metabolic Syndrome

In order to understand the current controversy, a little history is in order, we feel! Health care professionals and researchers have been aware for years that several risk factors for cardiovascular disease often appear in the same individual. The cluster of CVD risk factors most notably includes obesity, type 2 diabetes, hyperlipidemia, hypertension, and insulin resistance. Beginning in the late 1960s, investigators began proposing a unique pathophysiological condition underlying the CVD risk factor clustering. They called the condition the metabolic syndrome or insulin resistance syndrome. 1988 marked the publishing of Gerald Reaven's Banting Medal award lecture on insulin resistance, in which Reaven proposed that insulin resistance was the underlying cause of much CVD and that insulin resistance and hyperinsulinemia predisposed patients to hypertension, hyperlipidemia, and diabetes. Since then, metabolic syndrome has been recognized and defined by institutions such as the World Health Organization and the National Cholesterol Education Program, and it has been given an ICD-9 code.

This year, nearly two decades after his Banting Medal award lecture, Reaven published a review in which he concluded that diagnosis of the metabolic syndrome is not clinically useful and does not increase pathophysiologic understanding. In his direct words, "deciding that individuals do not have it [the metabolic syndrome] because they fail to satisfy three of five arbitrarily chosen criteria may withhold relevant therapeutic intervention." We completely agree with this, but also believe that the diagnosis – or at least, a warning signal! -- is useful because when individuals *do* satisfy three of the criteria, a little more concern may emerge in the average patient. Data from the The Casale Monferrato Study, which evaluated the ability of the WHO definition of the metabolic syndrome to predict all-cause and cardiovascular mortality in over 1500 type 2 diabetic patients, indicated that categorization with the metabolic syndrome does not predict CVD mortality in patients with type 2 diabetes any better than its single components predict CVD mortality. That said – we think patients may pay more attention to metabolic syndrome as a term than they do to "high blood pressure," etc. While we don't know that it'll actually change behavior, it might have a good chance of raising concern broadly.

[4] Grant RW, Buse JB, Meigs JB (for the University HealthSystem Consortium Diabetes Benchmarking Project Team). Quality of Diabetes Care in U.S. Academic Medical Centers: Low rates of medical regimen change. Diabetes Care 2005 28: 337-442.

So What?

While there is much information missing about the metabolic syndrome and much uncertainty in its definition, the syndrome as a term still has certain merits in our view. As certain clinical features indisputably tend to occur together in individuals who are at an increased risk for heart disease, it is important to investigate the underlying pathophysiological cause(s) of this clustering. In this respect, the metabolic syndrome is a useful construct for calling attention to the fact that several CVD risk factors tend to occur simultaneously and for prompting the search for other factors once one has been identified in an individual.

Why do we care so much about this? We see two important advantages of the diagnosis. First, compliance is a very problematic issue in medicine, especially for patients taking multiple pills, such as those who have for multiple clinical conditions (as represented by the metabolic syndrome). Medication that can treat more than one condition (on the extreme end of the spectrum, a medicine for the metabolic syndrome) would likely have the advantage of improving medication adherence. A safe and effective treatment for metabolic syndrome, if it can be developed, would have the power to help an immense number of people. Secondly, a diagnosis of metabolic syndrome serves as a wake up call generally and would be likelier to prompt fast-track to early treatment in individuals at high risk for CVD. The metabolic syndrome diagnosis raises questions about what these risk factors mean and when and how they should be treated, and we hope that the controversy will spur research that will shed light on these increasingly relevant and important questions.

-- By Katelyn Gamson, Erin M. Kane, and Kelly L. Close

4. **NAASO Review, Oct 15- 18, Vancouver: Stellar Meeting**

- **Lots of interest again**: There were ~2000 people at NAASO this year (c.f., 1700 pre-registered), potentially a few more than in Las Vegas a year ago, and although the number of exhibitors is the same (about 50), they sold substantially more space ~ bigger budgets equate to bigger exhibits. Even the Sanofi one a year ago was small (hard to imagine). So far, the sessions with the biggest attendance are associated with Sanofi's Acomplia. Broadly speaking, there's more discussion of clincial approaches beyond diet – notably drugs *and* bariatric surgery - this year compared to last.
- **Indeed, endocannabinoids are *the* compound of the meeting – though no new data, per se, there have been two major opportunities to learn more, and these have been standing room only-ish.**
- **We report below on our top ten items of interest:**
    - **#1: Pharmacotherapy for Obesity: State of the Art Views from Researchers, Industry, and Regulators**
    - **#2: The Endocannabinoid System in the Control of Energy Balance and Metabolism**
    - **#3: Sanofi-Sponsored Symposium: Cardiovascular Risk Reduction: Focus on Managing Cardiometabolic Risk Factors**
    - **#4: The President's Address**
    - **#5: Economics and Reimbursement for Bariatric Surgery**
    - **#6: Metabolic Syndrome**
    - **#7: Bariatric Surgery & Metabolic Change**
    - **#8: State-of-the-Art Pharmacotherapy**
    - **#9: The Role of Physical Activity in Weight Loss**
    - **#10: Posters & Exhibitions**

- **#1: Pharmacotherapy for Obesity: State of the Art Views from Researchers, Industry, and Regulators.** This three-hour session featured the following five presentations, several of which were highly basic-science focused and examined drug targets that were hypothetical, or in very early stage in development.
    - Gut and Gut/Hypothalamic Targets for Obesity Pharmacotherapy, Judith Korner, MD, PhD, Columbia: Neuroendocrine Unit
    - CNS Targets for Obesity Pharmacotherapy, Randy J. Seeley, Dept. of Psychiatry, Genome Research Institute Univ. of Cincinnati
    - Energy Expenditure/Adipose Regulators as Targets for Obesity Pharmacotherapy, Dr. Marc L. Reitman, Merck
    - Phase 2 and Phase 3 Drugs, Dr. Elliot Danforth, University of Vermont:

        - The most relevant presentation of these, unsurprisingly, was Danforth's, and the focus on phase 2 and 3 drugs.
        - *Danforth was positively giddy about rimonabant.*
    - In his introduction, Danforth noted that he has "*yet to see a designer drug based on new targets and new information*." In other words, he found all of the five drugs about which he spoke to be drug classes we already know about (lipase inhibitor, serotonin link) or in the case of Symlin, a "sort of an accidental weight loss discovery."
        - Danforth is yet another one who proclaims metabolic syndrome a misnomer. He prefers the term "*adipose tissue failure*." Doctors know about renal failure and heart failure, he argued, so why not adipose tissue failure? It's adipose tissue that's not doing its job, and its failure to contain fat is leading to insulin resistance, inflammatory cytokines, etc. This was a new platform in the ongoing metabolic syndrome debate. Now instead of for and against, we have for, against, and for with revision. This was pretty convincing.
        - He discussed the following drugs and targets:
            - Alizyme's version of Orlistat/Xenical called Cetilistat – this was characterized as a "'me too' lipase inhibitor"
            - Amylin's Symlin – as noted, he termed Symlin a "new anti-diabetic drug." Symlin delays gastric emptying and binds to several locations in the brain. Later studies showed an impressive weight loss, with a 240 microgram dose leading to a 4 kg loss over 24 weeks (DCU note – 240 mcg probably equates to four vials a month). Danforth noted that a Phase 2b study of this dose has been started.
            - Metabolic Pharmaceutical's growth hormone, AOD9604
            - Arena's ADP356-003, a serotoninweight control drug
            - Sanofi-Aventis' rimonabant. Danforth didn't appear bothered by the side effect profile. This continues to fascinate us – the small number of doctors with whom we have spoken about the CNS issues either express significant concern *or* seem to not worry about it much at all. It makes us a bit nervous.
    - Challenges to Drug Development, Steve Heymsfield, Merck

- **#2: The Endocannabinoid System in the Control of Energy Balance and Metabolism:** This session was highly focused on basic science and our current understanding of signaling pathways and the role of various hormones. It was, not too surprisingly, packed—people lined the walls and filled every seat in the large lecture hall. The speaker line up included the following:
    - Dr. Vincenzo di Marzo (Istituto di Chimica Biomolecolare, Italy), on the central and peripheral control of energy balance by the endocannabinoid system, a nice overview of its involvement in energy regulation;
    - Dr. George Kunos (Virginia Commonwealth University), whose presentation was titled "Coordinated Regulation of Energy Intake and Metabolism by Endocannabinoids" and who stressed knowledge we've gained from rat models;
    - Dr. Jeff Tasker (Tulane), who focused the most on detailed pathways, giving a talk titled "Rapid Crosstalk Regulation of ECB Release in the Hypothalamus by Glucocorticoids and Leptin"; and
    - Dr. Luc Van Gaal (University Hospital, Antwerp, Belgium), who presented the combined RIO results from rimonabant trials to the obesity community. Although the RIO data wasn't new, per se, much of the audience (probably most) hadn't seen it before, and there was clearly very high interest. In the Q&A, an audience member said, "*Your presentation was unambiguously positive. Is there any downside at all?*" This provoked laughter from the audience, and Dr. Van Gaal simply replied that it would be important to choose the right patient, at which point the inquisitor queried as to who would be the *wrong* patient for this drug. Dr. Van Gaal mentioned (in what could only be termed a concession) that the morbidly obese may not be appropriate. There were questions about the side effect profile, and overall we saw less concern than we would have expected. He did discuss HAD data that we hadn't heard before – this is "the Hospital Anxiety and Depression Scale" and showed that the placebo and treated groups had roughly the same score – since this doesn't reflect all the drop-outs in the trials, we are cautious on interpretation.

- **#3: Sanofi-Sponsored Symposium: Cardiovascular Risk Reduction: Focus on Managing Cardiometabolic Risk Factors:** Current president of NAASO, Dr. Louis Aronne, chaired the evening. The

audience polling showed audience specs: 34% obesity specialists, 7% diabetes, 6% CVD disease, 8% generalist and 44% research. 62% were from the U.S. and only 8% came from Canada, with 30% claiming "other." Of course, these stats don't show the percentage from industry, which was undoubtedly high.

- **Dr. Steve Haffner delivered an excellent presentation titled "Interrelationship between Cardiometabolic Risk Factors and the Development and Progression of Cardiovascular Disease Diabetes."** He showed the relationship between weight *gain*—as distinguished from weight—and type 2 diabetes, and he reviewed the results of INTERHEART, a case-controlled study of myocardial infarction. Dr. Haffner highlighted abdominal obesity as a very important risk factor, noting that it's even *more* highly correlated with cardiovascular risk than BMI. Although the correlation between BMI and abdominal obesity is very high, it's not 1. He stressed that one of the valuable lessons of INTERHEART is that the same factors predicted the prevalence of CHD regardless of the geographic region. In his assessment of risk factors, Dr. Haffner showed that HDL, blood pressure, and diabetes have the highest predictive value for CVD disease. The final element of Dr. Haffner's presentation that reminded us of themes we saw at EASD was his discussion of non-alcoholic fatty liver disease. Fatty livers are associated with obesity and insulin resistance, and we've seen rising interest in this condition.
- **Dr. Steven Smith presented "Importance of Diagnosing and Treating the Metabolic Syndrome in Reducing Cardiovascular Risk."** More focus here on the controversial MS definition; Dr. Smith notes that research suggests that these patients have risk for CVD above and beyond the summation of the individual factors. Dr. Smith conceded that the definition of this has been confusing, and his last slide set out a definitive description. According to this, metabolic syndrome: a) is associated with fat deposits throughout the body (the liver, the muscle, the beta cell, and the vessel walls), b) occurs in obese *and* nonobese patients, c) predicts the development of type 2 diabetes and CVD, and d) is useful in clinic to identify individuals at high metabolic risk.
- **Dr. F. Xavier Pi-Sunyer continued with "Use of Drug Therapy and Lifestyle Changes Treatment Plans in Controlling Cardiometabolic Risk Factors."** Dr. Pi-Sunyer reviewed what is known about Orlistat (Roche's Xenical) and sibutramine (Abbott's Meridia) as well as phentermine. He also alluded to endocannabinoid blockers, explaining that these compounds bind to the endocannabinoid receptor CB1 and CB2, and in blocking these sites, they reduce food intake and cause weight loss, even beyond what is attributable to the reduced food intake. Dr. Pi-Sunyer cited GLP-1, pramlintide, zonisamide, and bupropion among drugs not developed or approved for weight loss that have been shown to provide a beneficial effect on weight loss.
- **Concluding with a talk titled "Potential Role of New Therapies in Modifying Cardiovascular Risk in Overweight Patients with Metabolic Risk Factors,"** Dr. Michael Jensen touched on several "cutting-edge therapies." In an opening audience quiz question designed to show the growing range of approaches to treat obesity he asked which was *not* a target for obesity intervention: stimulation of the vagus nerve, a modification of growth hormone, or the endocannabinoid system – of course, 'none of the above' was the answer revealed. On the horizon, Dr. Jensen identified some devices: those related to gastric pacing and others dependent on vagus signal nerve modulation. Regarding compounds in development, he suggested that compounds are being pursued to a) regulate appetite, b) regulate appetite plus induce a beneficial metabolic effect, c) increase energy expenditure and fat oxidation, and d) decrease food absorption. In terms of appetite regulation, pure CNS drugs block appetite stimulation signals and stimulate appetite suppression signals. Peripheral drugs affect metabolic processes. Drugs cited:
  - **Arena's APD356**
  - **Another pure CNS drug in development by a company called Shionogi is a Neuropeptide Y drug** and is in Phase 1 testing.
  - **Rimonabant also affects the CNS**, and it regulates appetite through the CNS effects and gives metabolic benefit through the peripheral effects.
  - **Thera Technologies has Th-GRF**, a growth hormone releasing factor. It is in different stages of development for a variety of conditions.
  - **Beta-3 agonists were hoped** to selectively stimulate nonshivering thermogenesis, thereby wasting energy. CL-316, 243 was studied in humans and found not to be promising, and no other drugs in this class are currently under investigation.
  - **Growth hormone agonist: AOD9604 is a** fragment of growth hormone that was developed to selectively stimulate lipid oxidation. Although it is a peptide, it can be taken

orally. (CC note- we've heard a bit about this recently and are interesting in learning more about why this peptide is not digested like most.) It is in Phase 2 trials.
    - Pioglitazone (Takeda's Actos) has been shown in non-diabetic patients to increase LDL particle size and is being tested in various pre-diabetes trials.

- **#4 – The President's Address: President Aronne's address showcased two real-world examples of how institutions—Kaiser Permanente and the VA—have designed and launched large-scale program strategies to deal with obesity**. As Aronne noted in his introduction, obesity is "at a tipping point"—no longer small enough to be relegated to the category of "individual problem," obesity is demanding attention from large institutions, including employers and government. Within the Kaiser membership, 4.4 million individuals are overweight and obese, about 53% of Kaiser's 8.2 members total (actually somewhat less than the estimated 65% of the U.S. population). *Apparently, for this group at Kaiser, health care costs rose by 36% last year, and drug costs rose by a stunning 77%.* We hope Byetta and Symlin land on their formularies soon – even if drug costs rise by a higher percentage, the real downside in increased costs is likely in actual dollars in overall costs, particularly hospitalization.
    - **One major takeaway of Dr. Caplan's Kaiser discussion** reinforced our beliefs about problems in primary care, especially related to reimbursement – this was that physicians *do not* address the problem and often fail to discuss it with their patients. From a survey of patients, Kaiser found that 97% of people with a BMI >30 and 84% of patients with a BMI between 25 and 30 believe that weight loss is needed *but* that in the group of patients with a BMI >30, just 41% said they had received advice about weight from a health care provider. Among the patients BMI 25-27, that figure was just under 20%, and for those with a BMI 25-27, just under 10%. Even considering many patients probably have a selective memory, this is still low!
    - **Along the same lines, a 5-year Hawaiian chart review found that, while on average, each patient is weighed four times per year**, they receive diet counseling only 0.3 times per year.

- **#5 Economics of Obesity** Dr. William Dietz of the CDC and Dr. Eric Finkelstein of RTI presented data on the costs of obesity and the role of economic incentives in battling the obesity epidemic, respectively.
    - Dr. Dietz provided an overview of "the economics of obesity," offering some compelling statistics in support of funding interventions. For instance, he cited a recent statement by GM that obesity costs GM $1500 out of the price of each new car (of *each* car!), and that they spend more on medical coverage for their population than they spend on steel to *manufacture* new cars. Increasing costs are being driven by chronic diseases, many of which are being driven by obesity.
    - In the face of significant spending, we are not necessarily spending our money wisely. A curve of life expectancy versus health care spending showed a flattening of the curve, indicating a clear drop in marginal utility for additional dollars spent. In Japan, half as much money is spent, but they have a much greater life expectancy. Investment in prevention may be cost beneficial.
    - Increasingly, costs are being shifted to employees. According to Dr. Dietz, we are close to the point where take-home wages are declining as a result of the increase in medical costs.
    - Dr. Finkelstein began with some economic perspective on why obesity is on the rise. Food is cheap and getting cheaper, and this is especially true for preprocessed foods. So-called "accidental exercise" (daily exercise not part of a planned workout routine), has dropped dramatically.
    - In an extremely interesting point, Dr. Finkelstein presented data about Americans' knowledge of the risks of excess weight. In a phone survey that inquired about individuals' risks for health problems and life expectancy, overweight individuals estimated higher relative risks. Obese individuals stated still higher relative risks, and the self-reported life expectancies were close to correct. Obese adults forecasted life expectancies four years less than healthy weight adults.
    - This study suggests that information-based interventions are likely to have limited impact. In contrast, obesity interventions that affect the costs and benefits of behaviors related to obesity may be more effective. Clearly, merely educating the public about the health risks is not going to lower rates of obesity; we'd certainly love to see more economic incentives.
    - Employers are more likely to get involved first, in Dr. Finkelstein's view, and he advocated for incentive-based health promotion programs – choices could vary from subsidizing a gym membership or giving points or money for physical activity, to cash payouts, discounts on insurance premiums, gift certificates, and time off with pay.

- **#6: Metabolic Syndrome** Dr. Steven Haffner presented on the hot topic of metabolic syndrome and its controversial definition in a presentation geared toward an academic audience that detailed the different definitions of metabolic syndrome as well as its clinical significance.
    - He divided the definitions into three different models:
        - 1- Environmental causes: This describes the model advocated by NCEP and IDF, which says that environmental causes are responsible for the epidemic of the metabolic syndrome. It calls for a treatment based on the obesity reduction and activity increases.
        - 2- Insulin resistance: The WHO definition suggests that insulin resistance is the "underlying cause" of metabolic syndrome. Here, insulin resistance is a requirement for metabolic syndrome, and is diet, exercise, and use of insulin sensitizers.
        - 3- Inflammation: This is another concept not attached to any one organization. It says that inflammation is the underlying cause of metabolic syndrome. In this case, the treatment is diet, exercise, and drugs - insulin sensitizers, statins, ACE inhibitors, and ARBs.
    - One of the more fascinating aspects of Dr. Haffner's presentation was his focus on motivation and understanding the origins of the definitions. For instance, NCEP is a lipid group, and two of their five criteria are lipid-based. Others might have suggested combining them into one category using an either/or listing. Dr. Haffner also noted that many companies latched onto the WHO definition because it was more "pharmacological friendly."

- **#7: Bariatric Surgery & Metabolic Change** The most cutting-edge research in the field of bariatric surgery right now is investigating why the surgery is so effective—and the answer is not because the size of the stomach is limited. Rather, hormonal control of appetite and weight changes dramatically, and researchers are working to understand how and why. In addition to our notes from a NAASO presentation on the topic, we include below some takes from a fascinating interview with Dr. Guilherme Campos of the UCSF Bariatric Surgery Program.
    - Dr. Francesco Rubino presented at NAASO on "The Role of the Intestinal Foregut in Diabetes Resolution and Appetite Control after Gastric Bypass Surgery"
    - Dr. Rubino attempted to elucidate the hottest question regarding bariatric surgery, which is: what exactly is going on? As one internist told us, "as usual, the surgeons got the right answer with the wrong idea." What began as an attempt to induce weight loss by reducing the size of the stomach has been found to have unbelievable metabolic impact. It seems that many of the gut hormones—ghrelin, CCK1, PPY, GLP-1, leptin, alpha-MSH, HOMA-IR, others—change dramatically after the surgery, generating much of the positive effect.
    - In fact, the restricted stomach pouch is not a major factor in the weight loss seen after gastric bypass. In another surgery, gastric banding, there is restriction but no rerouting or short-circuiting in the stomach—and it is not nearly as effective.
    - In gastric bypass, 95% of the stomach, the whole duodenum, and the first part of the jejunum are bypassed. The procedure is very effective, but there is little knowledge about the mechanism of action. Many experiments are being done in Zucker rats to try to understand what hormonal changes are important and how these are induced with the surgery. So far, it's very unclear.
    - Perhaps the most astounding metabolic effect of gastric bypass is that patients with type 2 diabetes no longer have it after the surgery. This happens immediately, not progressively in conjunction with weight loss. Dr. Rubino stated that sometimes this happens before people leave the hospital. 83% of diabetic subjects have euglycemia up to 14 years later.
    - Dr. Rubino approached the topic carefully, saying, "I don't know if this is a cure, but if it's not, it looks very close to that kind of concept." He explained that it raises the question: is type 2 diabetes an operable disease? He noted that this question might antagonize diabetologists, and he showed a photo of a kitten (the surgeons) surrounded by a pack of Dobermans (the diabetologists).

- **#8: State-of-the-Art Pharmacotherapy** This multi-segment session examined clinical trial data for novel compounds and some preexisting compounds now being investigated for obesity therapy.
    - **"Effect of APD356, a Selective 5-HT2C Agonist, on Weight Loss in a 4-Week Study of Healthy Obese Persons" Dr. Steven Smith**
    - APD356, manufactured by Arena and in phase 2 trials is a serotonin agonist that activates the 5-HT2C receptor in the hypothalamus, resulting in reduction of food intake and weight loss.

- Dr. Smith presented the results from a four-week study of 352 volunteers with a BMI between 30 and 45. Patients received 1, 5, or 15 mg of APD356 for 28 days once daily and were instructed to maintain their normal diet. There was a highly statistically significant weight loss of 1.3 kg in the 15 mg group versus 0.3 kg in the placebo group. The drug was well-tolerated, and special attention was paid to the echocardiograms, because of the historical heart complications associated with serotonin inhibitors.
- **"Progressive Reductions in Body Weight with 82 Weeks of Exenatide Treatment in Overweight Patients with Type 2 Diabetes" Dr. Lawrence Blonde**
- Dr. Blonde presented an 82-week study of exenatide on 393 patients with type 2 diabetes. Patients included in the cohort were those enrolled in three different 3-week studies, followed by a 52-week open-label extension. Patients were those failing to achieve glycemic control with either sulfonylureas, metformin, or a combination. Patients were randomized to placebo, 5 μg, or 10 μg.
- Patients continued their prior oral therapy, and results on weight were similar in each group. At 30 weeks, the average weight in the placebo group had changed by -0.6 kg versus -1.9 kg (4 lbs) in the 5 μg arm and -2.7 kg (6 lbs) in the 10 μg study. Patients on exenatide from that point received the 10 μg dose. The weight loss continued progressively to 82 weeks, at which point total weight loss was ~-4.5 kg (10 lbs) for the group that had been on 10 μg for the study duration.
- We love quartile data – so much more granular. One could say that 10 pounds isn't that much for someone truly overweight (true, but for them, it's much preferred to gaining insulin – associated weight), but additional data showed that for participants in the top quartile of weight loss, the average 82-week weight loss was between 10.3 kg and 12.2 kg (23 lbs - 27 lbs). As expected, those participants with a greater initial BMI lost a greater amount of weight.

- **"Perceptions of Appetite and Weight Control Associated with Weight Loss in Pramlintide-Treated Obese Subjects" Dr. Vanita Aroda**
- Dr. Aroda presented the results from a study that evaluated obese participants' views of pramlintide at the conclusion of a phase 2 study. At 16 weeks, those subjects treated with pramlintide had lost an average of 3.7 kg (about 8 lbs.).
- Survey responses showed that 72% of the 7pramlintide group found that it helped them control their appetite (versus 31% in the placebo group); 63% said it helped them control their weight (versus 24% in the placebo group). Strikingly, 61% said that the benefit outweighed the inconvenience of injections and 76% said that the benefit outweighed any side effects. These figures were 43% and 52%, respectively, in the placebo group.

- **"The Effect of AOD9604 on Weight Loss in Obese Adults"**
  Metabolic Pharmaceuticals Caroline Herd
- AOD9604 is a 16 amino acid synthetic peptide fragment of the C-terminal region of human growth hormone, manufactured by Metabolic Pharmaceuticals, an Australian biotech.
- The rationale behind the creation of the once-daily oral drug was that obese people have 75% lower levels of circulating growth hormone, which may be an adaptation to maintain obesity.
- In the short term, investigators have seen a 0.5 kg fat loss per week but an equal gain in lean tissue mass, so that they are seeing no net change in body weight.
- The smallest dose of 1 mg had the greatest weight loss of 2.8 kg versus 0.8 kg for the placebo – significant in women, but not the entire group. There was a non-linear dose response curve, so that the weight loss did not increase as dosage increased. As a result, the next trial—a 500-subject phase 2 study titled OPTIONS—will test dosages smaller than 1 mg. We basically wouldn't have really paid attention to this except that we learned that at the conclusion of the study, fewer participants in the treatment group had developed diabetes, and there was a reduction in the proportion with impaired glucose tolerance.

- **#9: The Role of Physical Activity in Weight Loss**
  - The most striking take-aways from Dr. Wyatt's presentation were 1) that patients who exercise and diet do not have substantially greater rates of weight loss than patients who rely only on caloric restriction; and 2) exercise is the single greatest predictor of weight maintenance. Patients who do not have adequate physical activity cannot maintain a weight loss.

- Exercise alone would produce a weight loss of only 0.06 – 0.1 kg per week, although there is a dose-response relationship. In one study where participants exercised 10 hours per day, they were able to lose 1.8 kg/wk.
- One prospective study of weight loss randomized patients to two levels of activity: 1000 kcal/wk versus 2500 kcal/wk. At six months, the amount of weight loss was similar; at 18 months, however, the group with greater physical activity had significantly less weight gain.
- Wyatt suggested that this might mean patients should pursue different strategies for weight loss vs. weight maintenance, but acknowledged the importance of established exercise habits.

- **#10: Posters & Exhibitions** Most interesting exhibits/posters were Medtronic, sanofi-aventis, and Amylin.
  - Medtronic: Far and away the most interesting booth, and well positioned at the entrance. This was one of the few booths actually staffed by representatives from the company, rather than staff members from the exhibition hall merely handing out literature, and no doubt the extra effort was put in to raise awareness about Medtronic's new gastric pacing device. The "Transcend Implantable Gastric Sensor" was on display, and Close Concerns examined the device, an implantable pulse generator that delivers "small bursts of electrical pulses through the lead to the stomach wall." Medtronic acquired Transcend in July, having worked with the smaller company on device production since 2001, and the device is approved for use in Canada and Western Europe. It is not yet approved for use in the U.S.
  - More on "Transcend": The clinical studies appear to have been done in patients with enormously high BMIs: a small (n=4!) study enrolled patients with BMIs ranging from 52 to 58. A pilot study of 10 patients included those with BMI >40. Rates of weight loss were given as percentage of excess weight lost (EWL) and were at about 25%. The larger post-marketing trial in Europe, which has enrolled 47 patients, has demonstrated progressive weight loss: 21% EWL at six months, continuing to 33% EWL at 36 months.
  - Research into the mechanism of action is ongoing. Gastric pacing works by stretching the stomach to induce early satiety. There is also hypothesized to be an effect on hormones (leptin, CCK, GLP1, ghrelin) and brain signaling, though the information on this is vague.
  - sanofi-aventis: The fact that this booth had no company personnel was bizarre, but the exhibition hall hirees gave out thick packets on "cardiometabolic disease and adipose tissue: understanding the link." The company certainly has gotten the message out about metabolic syndrome during this conference, and the obesity audience seems well primed for the launch of rimonabant. Now – we're eager to see what happens at panel . . .

  - **Posters of Special Note**
  - **#1 Rimonabant: Changes in Body Composition among Dyslipidemic Overweight/Obese Patients Treated with Rimonabant: The RIO-Lipids Trial**
  - Although the data from RIO-Lipids are not new, this study assessed exactly *what kind* of body mass is lost in patients treated with rimonabant. The posters showed that lean body mass was not significantly reduced, and changes in waist circumference were highly associated with changes in fat mass. There were significant reductions in total body fat and in fat mass both in the trunk and the extremities, and these changes were significantly correlated with changes in metabolic parameters in patients in the treatment group. The trial supported, of course, the hypothesis that weight loss resulting from rimonabant administration represents a loss of body fat.

  - **#2 Pramlintide: Characterization of Obese Subjects Achieving 5% of Greater Weight Loss After 16 Weeks of Treatment with the Amylin Analog Pramlintide**
  - This study was the initial Phase 2 study in obese subjects reported on in Prague last summer. It tested the use of Symlin in 204 obese subjects, who had an average BMI of 38.
  - **The study was designed as a 16-week placebo versus pramlintide trial**, with 2/3 of the subjects assigned to pramlinide. In the first four weeks of the study, participants could gradually increase the dosage up to 240 µg.
  - **On average, those in the pramlintide group lost 3.7 kg (8 lbs).** 31% of subjects achieved a weight loss greater than 5% of their body weight, and in this group, the average weight loss was a more impressive 7.6 kg (17 lbs). This subgroup of stronger responders decreased waist

circumference by an average of 7.6 cm, while the weaker responders lost an average of 2.9 cm in waist circumference.
    - **The patient satisfaction showed that pramlintide helped control appetite,** with 64% of the subgroup of patients who lost <5% agreeing that pramlintide helped control appetite and in the group of stronger responders, 92% said that it helped control appetite.
    - **Most patients believed that "the benefits of study medication outweighed any side effects."** 70% of those who lost <5% agreed with this statement compared to 92% in the subgroup that lost >5% of body weight. Overall, 31% of pramlintide-treated subjects achieved a greater than 5% weight loss, compared with 2% of placebo-treated subjects.

    - **#3 Exenatide: Exenatide Reduced Body Weight Compared to Insulin Glargine in Metformin and Sulfonylurea-treated Patients with Type 2 Diabetes**
    - This head-to-head analysis of a 26-week treatment of glargine versus exenatide included 549 patients at 82 sites in 13 countries. This was similar to what had been reported on at ADA - **the change in A1c between glargine and exenatide was similar**, with both lowering A1c from a baseline of approximately 8.2% to approximately 7.2%. **In contrast, the weight change between the two groups differed by approximately 4.4 kg (9 lbs).** At 26 weeks, those on exenatide had lost an average of 2.3 kg (5 lbs), while those on glargine gained approximately 1.8 kg (4 lbs).
    - **In terms of the effect of nausea on weight loss,** an analysis stratified according to whether or not the patient experienced nausea showed similar reductions in weight loss. Those experiencing nausea lost an average of 2.4 kg, while those not experiencing nausea lost an average of 1.9 kg.

- **Misc: We heard in casual conversation as well as the formal presentations time and time again - physicians are ignoring obesity**. One Canadian GP we spoke to attributed it to a) a lack of time and cost restraints, and b) a lack of a clear-cut treatment plan or algorithm to approach what has become a very serious issue for many patients. The statistics in Dr. Caplan's Kaiser presentation underscored this, with only 40% patients in the obese range (BMI>30), saying that their physician had spoken to them about their weight. In the overweight range, this figure dropped to 10-20%.

Want more details, especially on the pharma front? So did we, and we asked a lot of questions! Detailed notes will be available in Diabetes 2006 – more information coming on that in December.

--by Erin M. Kane and Kelly L. Close

5. **Canadian Diabetes Meeting, Oct 19-22, Edmonton**:
Following Vancouver for NAASO, we went to Edmonton for the annual meeting of the CDA. We report here on our top learnings:

- **Medtronic symposium: Achievement of Treatment Goals Combining Real-Time Glucose Sensing and Insulin Pump Therapy**
- **Merck symposium: Management of Metabolic Syndrome**
- **Biovail Pharmaceuticals symposium: ACT: An Interactive Discussion on Adherence & Control in the Treatment of Type 2 Diabetes**
- **Future Therapies for Type 2: GLP-1 and DPP-IV.**
- **Islets, Stem Cells, and Hypoglycemia**
- **Sanofi symposium: Advances in Metabolic Control**
- **Glaxo-Smith Kline symposium: The Role of Insulin Resistance in the Development and Progression of Type 2 Diabetes**
- **Debate on the Early Use of Insulin in Type 2 Diabetes**

Top Five Themes of CDA 2005:

1. **Canadians believe in insulin for type 2, and they want more of it, earlier, now.** Dr. Hertzel Gerstein is a particularly outspoken supporter of this, and we saw him speak on the topic at the sanofi-sponsored symposium the night before he debated about it with Dr. Jean-Louis Chiasson. We saw some impressive data on this point suggesting that insulin enhances patient efficacy and allows for quicker titration than with

oral meds. It is going to be extremely interesting to watch the entry of incretins and to see how treatment patterns change – since Byetta isn't yet available in Canada, it was difficult to gain much closer on this.

2. **Diabetes is 'glucose-centric', and it may be time for that to change.** Diabetes care has historically concentrated on achieving glycemic control, particularly since DCCT/UKPDS and this is clearly undergoing some degree of change. Type 2 diabetes is morphing into something much greater than hyperglycemia, and increasing attention is being paid to lipid problems and cardiovascular risk. This merging of cardiovascular and metabolic has sparked turf wars between specialists.
3. **Cardiology and diabetes are merging.** Seventy percent of patients with diabetes die from cardiovascular disease, and cardiologists and endocrinologists are becoming more and more intertwined. Dr. Gerstein joked that cardiologists may need to learn to prescribe insulin, and we heard of one primary care physician who addressed lipids problems first and glycemic control second.
4. **More non-physician personnel are engaged in diabetes care in Canada.** Unlike in the U.S., Canada does not have a separate diabetes meeting for educators, nurses, and dieticians, and the composition of the meeting was estimated by CDA staff to be less than 40% physicians and researchers, with the other 60% non-physician clinicians.
5. **'Adherence' was a buzzword at this year's CDA. This is a nice way of saying compliance.** There is growing interest in combining oral medications into one pill and cutting down on the number of pills patients must take as a key to adherence and improved control.

- **#1: Medtronic Symposium: Achievement of Treatment Goals Combining Real-Time Glucose Sensing and Insulin Pump Therapy**

  - **Dr. Ian Blumer chaired the session and began with some background on both treatment targets and new glucose sensing technology.** The CDA has set its treatment goals at an A1C <7. In terms of technology, first introduced non-real-time continuous glucose sensing, and a hand-raising poll showed that about 1/3 of the people in the room had had experience with that. Dr. Blumer described real time systems as well, with the suggestion that the open loop system was the next step.
    - In terms of accuracy, it was noted that CGMS is within 10-15% of a plasma glucose sample during euglycemia and hyperglycemia, but that accuracy declines during hypoglycemia and during rapid fluctuations in blood glucose.
    - **He also spoke to the projected cost.** He cited estimates of $3300 for both the real-time (Guardian RT - the sensor that sends data and the receiver) and the non-real time (CGMS), quoting $50 for disposable sensors (figures were Canadian dollars).
    - **In terms of clinical utility**, hypoglycemia warning was mentioned as a benefit as well as knowledge of what variability is present for a given A1C. He noted that it will be also useful for having a global measure of averages when waiting for the A1C is not viable—as in pregnancy.
    - Concluding, he observed that continuous glucose sensing is "not ready for continual home use for most people with diabetes" but that it is "ready as a helpful complementary tool used for occasional use in certain people with diabetes."
- **#2 Merck: Management of Metabolic Syndrome**
    - This session was extremely well attended, especially given that it was the first session of the conference. The panel featured presentations by pharmacist Scott Simpson (University of Alberta), endocrinologist Richard Lewanzcuk (University of Alberta), and CDE Dorothy Smolek (Regional Diabetes Program). We highlight here four major take-aways from the symposium:
    - **The involvement of non-physician personnel is key.** The pharmacist highlighted a Canadian study that showed that the average diabetes patient in Saskatchewan sees their pharmacist 14 times per year, while they see a specialist only one time a year on average. As such, the pharmacist has a unique opportunity to help diabetes patients, and in Canada, many pharmacists choose to specialize in diabetes by becoming CDEs as well. We hear a lot about the transfer of responsibilities to non-physicians in the U.S., but in Canada, they're already there.
    - **The complexity of medications is a challenge in the treatment of diabetes.** The pharmacist highlighted as well that they can take responsibility for monitoring for drug interactions, as physicians increasingly need to prescribe multiple, multiple medications for diabetes patients: medications for glycemic control, hypertension, cholesterol, etc. He noted physicians sometimes fail to pursue aggressive therapy because of the complexity of medication management.

- **Adherence is a major barrier.** This was a theme of Day One of the conference, and CDE Smolek highlighted ways to improve compliance (again, formerly known as compliance).
- **Metabolic syndrome could have implications for glucose monitoring.** We were surprised during the Q&A when one clinician asked whether blood glucose monitoring might be a useful tool for those with metabolic syndrome, as we had not yet heard this proposed. The expert panel seemed in general to believe that it was not necessary, referencing an IGT class taught in Edmonton that did not incorporate glucose monitoring. However, Dr. Simpson pointed out that self-measurement has been shown to improve patient adherence and suggested that glucose monitoring could be useful as a reinforcement tool for those with IGT/metabolic syndrome; he noted that a lack of reimbursement would likely prevent serious movement on this front.

- **#3 Biovail Pharmaceuticals: ACT: An Interactive Discussion on Adherence & Control in the Treatment of Type 2 Diabetes**
  - Dr. Lawrence Leiter (University of Toronto, St. Michael's Hospital) moderated the session. Dr. Stewart Harris (University of Western Ontario) presented "A Primary Care Perspective on the Issues and Challenges in Glycemic Management," followed by "What Does the Evidence Tell Us about Glycemic Control and the Consequences of Type 2 Diabetes?" which was presented by Dr. Hertzel Gerstein (McMaster University). Diabetes educator Anne Belton joined the experts on stage for the Q&A. The topic of the symposium was adherence, through which Biovail was able to promote its new once-daily long-acting formulation of metformin, called Glumetza.
  - The main message of the first segment of the presentation was that 49% of patients with type 2 diabetes in Canada are not meeting glycemic targets, and that providers are relying too heavily on lifestyle. Dr. Harris emphasized that medications for glucose lowering and co-morbid conditions are necessary. Though providers seem to believe in lifestyle, control for patients worsens over time.
  - From there, Dr. Harris tackled the barriers to adherence, using the term "polypharmacy." A major barrier, according to some studies, is the frequency of dosing. Treatment adherence in one study published in the *American Journal of Medicine* was found to be 65-85% for oral medications and 60-80% for insulin. Another study showed that A1C increases with higher frequency of dosing of medications. Even more directly, a last study showed that as dosage increases, there is a reduction in adherence.
  - In sum, the presentation said that a) patients are not achieving targets, b) it's because they need more medication, c) that medication should be metformin, and d) their compliance will be better on a formulation with less frequent dosage—which is where Glumetza comes in.
  - Dr. Gerstein stressed the complications of type 2 diabetes, noting that UKPDS showed that improved control reduced diabetes-related outcomes. He stated as well that, while there is some support for it, we do not yet know conclusively whether lower glucose results in less cardiovascular disease. Major study results to be reported in 2008-2009 may elucidate this question, which will be important, as >70% of people with diabetes die from cardiovascular causes. We do know that glycemic control reduces microvascular disease. Diabetes reduces life expectancy by about 12 years.

- **#4 Future Therapies for Type 2 Diabetes** *This presentation titled "Future Therapies for Type 2 Diabetes" was chaired by Dr. Timothy Kieffer (University of British Columbia) and focused on GLP-1 and DPP-IV inhibitors. Although the session emphasized basic science, there was some discussion of the clinical trials and commercial development of these drugs. Dr. Daniel Drucker, Dr. Dariush Elahi, and Dr. Christopher McIntosh gave presentations.*
  - **Our Top Three Take-aways**
    1. The researchers who presented were extremely positive about the potential that GLP-1 increases beta cell mass. The first two presentations both spoke to the question of "memory," or the continued beneficial effects that continue after the drug is stopped, and they cited this as evidence that beta cell mass increases during therapy.
    2. From the final presentation on DPP-IV, it was clear that there are many concerns about the multiple effects of DPP-IV. As an enzyme that degrades substrates in that have cardiovascular and immunologic function, it is a high-risk drug target and audience members seemed wary.

3. From comments by the session chair, we gathered that clinicians are anxious for Byetta to be available in Canada.

- **Dr. Daniel Drucker (University of Toronto)**
  GLP-1 Receptor Activation for the Treatment of Type 2 Diabetes
  - Dr. Drucker prefaced his discussion with a brief overview of history of gut peptide hormones. Interest in gut peptide hormones heightened with the creation of an immunoassay for peptides, and the glucagon gene was cloned in the early 1980s. Glucagon-like peptides are formed by removing the first six amino acids to generate an active protein. GLP-1 increases a favorable beta-cell gene expression profile via several different pathways, and the master pancreas gene Pdx-1 is particularly important. Pdx-1 is a transcription gene that, when mutated in humans, results in failure to develop a pancreas.
  - Studies of the GLP-1 receptor using GLP-1 receptor knockout mice showed that they were more vulnerable to beta cell death when a beta cell toxin was administered. Knocking out this receptor impairs glucose-stimulated insulin secretion and results in abnormal glycemic excursions.
  - Dr. Susan Bonner-Weir has shown that exendin-4, a GLP-1 receptor agonist, increases beta cell mass in rats who have had a partial pancreatectomy. Four weeks after the last dose of exendin-4, rats continue to have lower blood glucose. As the compound breaks down quickly and is no longer present in the system, this indicates a memory effect. This suggests that the GLP-1 actually preserves islet integrity and reduces apoptotic cell death. We are waiting, of course, for confirmation in humans.
  - Another way to access this pathway is to inhibit the enzyme DPP-IV, as this enzyme degrades GLP-1 and GIP. Researchers have seen an enhancement of beta cell mass in animals treated with DPP-IV.
  - Dr. Drucker explained that excellent long list to the many people in the room who didn't seem familiar with GLP-1 – this compound stimulates insulin secretion, limits glucagon secretion, slows gastric emptying, and reduces food intake. In patients with type 2 diabetes, GLP-1 actions are glucose-dependent, which minimizes the risk of hypoglycemia (eliminates it in monotherapy).
  - In Q&A, one participant inquired whether GLP-1 therapies may lose effectiveness over time. Dr. Drucker noted that this does not seem to be the case in animal models, but that the durability in patients with diabetes is not yet known. He added that the critical question is whether these treatments will have more longevity than our current diabetes therapies.
  - Dr. Drucker maintains a website on GLP-1 and related therapies at www.glucagon.com.

- **Dr. Dariush Elahi (Johns Hopkins)**
  "The Insulinotropic, Insulkinotrophic, and Insulinomimetic Effects of Incretins"
  - Quoteworthy: "As Dan said, there is no such thing as a dead beta cell." Dr. Elahi and Dr. Drucker both emphasized the regenerative powers of these compounds. Though more data is needed on this point, if confirmed, these would be the first drugs shown to actually reverse the progressive failure of beta cells.
  - Dr. Elahi explained that GLP-1 can be useful in Type 1 diabetes because, although GLP-1 cannot stimulate insulin release, it lowers glucose by reducing hepatic glucose production.
  - Dr. Elahi also highlighted the memory effect of GLP-1. In other words, the fact that glucose is lowered after the drug administration stops indicates that the compound affecting the body in a longer-term way, perhaps by increasing beta cell mass.
  - Dr. Elahi referenced a study that compared treatment with GLP-1 alone to conventional treatment with metformin and sulfonylureas. Using 55 mg/dL as the cutoff for hypoglycemia, there were 84 incidents of hypoglycemia in the conventional treatment group and only one in the GLP group. The total number in the study was not mentioned.
  - GLP-1R agonists under development that were mentioned include Liraglutide, CJC-1131, Ave-0010, albugon, and GLP-1 transferin. Liraglutide is a modified version of GLP-1 in which the hormone is coupled to a fatty acid and can remain in the blood for eight to 15 hours.
  - At the conclusion of the presentation, the moderator (Dr. Kieffer) inquired as to whether anyone in the audience knew when exenatide would be available in Canada. He said he was "curious to know," and in the absence of an answer, said, "hopefully soon."

- **Christopher McIntosh (Univeristy of British Columbia)**
  Enhancing GLP-1 Action with Inhibitors of Dipeptidyl Peptidase IV: from Bench to Bedside
  - Looking at the pathway from a different angle, Dr. McIntosh explained that a DPP-IV inhibitor could obviate the need for injections. He mentioned that he had worked with Probiodrug of Germany to develop DPP-IV inhibitors. DPP-IV degrades both GIP and GLP-1.

- Dr. McIntosh spoke to the prevalence of DPP-IV in the body, noting that "virtually every organ you have has some DPP-IV in it." There are both membrane-bound and soluble forms. In the membrane, DPP-IV plays an immunologic role and is called CD26.
- This peptidase has a high specificity for N-terminal dipeptidyl, and it cleaves the peptide to make it non-insulinotropic.
- Dr. McIntosh reviewed major classes of inhibitors that have been tested in trials:
  - Reversible product analogs:
    - P32/98 (Probiodrug)
    - MK0431 (Merck)
  - Non-reversible
    - Dr. McIntosh warned against these and felt that they may be more dangerous. He noted that these irreversible compounds work throughout the day rather than just at mealtime.
- Regarding DPP-IV inhibitors in clinical trials, Dr. McIntosh listed the following:
  - Psn9301 in phase 2/3 (Prosidion, bought Probiodrug)
  - Merck in phase 3
  - Novartis in phase 3
  - BMS in stage 2
  - GSK in stage 1
- Vildagliptin (LAF 237) combined with metformin gives sustained improvement in A1C over one year.
- In terms of safety, Dr. McIntosh acknowledged that other hormones are reduced by DPP-IV and that there has been concern about this.
  - DPP-IV is pleiotroopic, and substrates of DPP-IV are involved in cardiovascular function, immune function, and pain regulation.
  - DPP-IV is a member of a broader gene family, and other related enzymes have physiological roles. Dr. McIntosh cited a 2005 paper published by Lankas et al in *Diabetes*: "in summary, these results strongly suggest that the inhibition of DPP 8 and DPP 9 are profoundly toxic." Thus, inhibition of other members of this enzyme family has been problematic.
- Dr. McIntosh also noted that "A patient likes to have one pill a day, but this may require two or three."
- In the Q&A, people inquired about tumor formation and cardiovascular changes. While Dr. McIntosh was obviously a champion of DPP-IV inhibitors, his presentation still contained many questions about their safety and possible unintended side effects.

- **#5: Islets, Stem Cells, and Hypoglycemia** *Dr. Greg Korbutt of the University of Alberta presented an update on the potential of human stem cells—both adult and embryonic—for use in people with diabetes. The leader of the Edmonton protocol, Dr. James Shapiro, discussed where we are in islet transplantation. Dr. Stephanie Amiel, one of the leading experts on hypoglycemia, presented intriguing research on understanding severe and recurrent hypoglycemia.*
  - **Gregory Korbutt (University of Alberta) - Use of Human Stem Cells for Diabetes Therapy**
  - Dr. Korbutt clarified that islet cell transplantation is not a cure for diabetes; rather, it replaces one form of therapy for another. Five years post-transplant only 15% of patients are insulin independent.
  - Furthermore, patients receiving these transplants must take immunosuppressive drugs. As such, children cannot be transplanted. The procedure is also not for type 2 patients and not for everyone with type 1. According to Dr. Korbutt, if a patient has tight control, they are better off with injections. To treat all diabetics with islet transplantation would require a) no drug therapy; and b) an unlimited source of islets.
  - **Focusing on potential sources of islet tissue**, Dr. Korbutt listed five theoretical options:
    - **Human cadaveric pancreata**: this is the most common source for today's islet transplantations, but there is limited availability.
    - **Animal pancreata**: animals breed rapidly and have large litters. This is an unlimited source, one that Dr. Korbutt identified as ethically acceptable, and indeed he believes this is the most promising source for the immediate future. However, there is currently a government ban on using pig organs in transplantation because of fears that they may transfer a virus.
    - **Fish brockman bodies**: essentially fish islet tissue.
    - **Engineered cell lines**: potentially engineering non-beta cells to become beta cells.
    - **Stem cells**

- **Adult stem cells**
  - These are present in skin, nerve, bone marrow, blood, liver, and brain. They are extremely difficult to identify, isolate, and purify.
  - We do not yet know how to differentiate these stem cells into a beta cell, and it is unknown whether there are significant numbers for therapeutic application.
  - Researchers are working to isolate mesenchymal stem cells (which are found in the bone marrow) to see if they can induce differentiation in to endoderm (the type of tissue that includes the pancreas). These cells have already been differentiated into osteocytes (bone) and other types of cells.
  - So far, researchers have been able to get cells to differentiate into hepatocytes (liver cells, which are a type of endoderm) and to express both genes and proteins for hepatocytes. They can turn on PDX-1, the master gene that controls the development of the pancreas, but have not yet been able to induce the production of insulin. Dr. Korbutt noted that they believe these cells are capable of becoming insulin positive cells, but that the protocol for differentiation needs to be refined.
- **Other sources stem cells**
  - Fetal stem cells: this kind of research faces heavy regulation in Canada. Like adult stem cells, use of these would require expansion.
  - Cord blood: no ethical objection, but does not seem very promising at this time.
- **Embryonic stem cells**
  - These are pluripotent, meaning that they can differentiate into many different kinds of cells, and they can be expanded indefinitely. There are ethical complications with this source of stem cells.
  - **The main source of embryos** are discarded embryos from IVF clinics. In the UK, it is possible to use the fertilization of donated oocytes. Somatic cell nuclear transfer is also an option, in which the DNA from any kind of cell in the body is inserted into an oocyte that has had its DNA removed. This is not legal in Canada or the U.S., and though Dr. Korbutt did not use this word, is the definition of human cloning.
  - In a very recent article in Nature, scientists announced that they were able to extract one cell from an embryo and expand it into embryonic stem cells without destroying the embryo.
  - Currently in Dr. Korbutt's lab, investigators are working with embryonic stem cells. They have done transplants in animals and have not been able to cure diabetes. They have, however, had some success in getting cells that produce insulin and glucagon.
  - The biggest problem so far is that teratomas form post-transplant. Even if there are only a few undifferentiated cells at the time of transplantation, these can turn into tumors. Researchers must also solve the supply problem and find strategies to prevent rejection.
  - In the Q&A, questions focused on possible solutions to the tumor problem and xenotransplantation. Dr. Korbutt: "My feeling is that xenotransplantation is going to be the first thing that will solve the supply problem, but we have to be sure we're not going to transmit a virus." They have monkeys over six months post-transplant that are completely insulin-independent.

- **James Shapiro (University of Alberta) - Islet Cell Transplantation**
- Dr. Shapiro began with the history of islet transplantation. He noted that the Edmonton protocol in the year 2000 improved insulin-independence one-year post-transplant from 8% to 100%. Overall, transplants have been done in more than 550 patients at more than 50 institutions worldwide.
- Recent updates: 1) The University of Minnesota recently performed a successful transplant with a **single donor** (usually the procedure requires multiple donors for one transplant); 2) In Kyoto, a **living-donor** transplant was recently successful. Though this may be a solution to the supply problem, Dr. Shapiro was very cautious about the need to be sure the donors do not become diabetic.
- To quality for a transplant, patients must have type 1 diabetes and be already on immunosuppression. If they are not already on immunosuppression, they must meet strict criteria: usually several episodes of severe hypoglycemia, hypoglycemia unawareness, and marked glycemic lability. Of 1700 who have been screened for a transplant at Edmonton, only 6% have qualified.
- In terms **of outcomes,** 82 patients have been transplanted, and 70-80% achieved euglycemia post-transplant. There is an "inexorable" loss of insulin independence, which drops down to 11% at five

years. However, patients' C-peptide levels remain at 82%, and they continue to see benefits in their A1C as well as some endogenous insulin secretion.

- **Investigators are working to understand the decay in islet function over time.**

- **Dr. Stephanie Amiel (King's College, London) - Brittle Diabetes/Hypoglycemia: Why So Difficult?**
- **The main question of Dr. Amiel's talk was whether hypoglycemia is the result of "difficult diabetes" or "difficult patients."** The term 'brittle diabetes' has been used to refer to patients who have extreme hyperglycemia/frequent DKA as well as those with severe and recurrent hypoglycemia. In the case of hyperglycemia, experts have decided that this has a psychological cause and that it is the result of self-harming behavior.
- **In terms of definitions**:
    - Whipple's triad still defines hypoglycemia: symptoms of low BG, measurably low BG, and symptoms relieved by the administration of glucose.
    - The ADA threshold for hypoglycemia is 4 mmol/L (72 mg/dL), but Dr. Amiel prefers the definition of 3.5 mmol/L (63 mg/dL), as this is where the counterregulatory physiological responses begin.
- **People with diabetes have defective counterregulation.** In a normal person falling glucose shuts down insulin production and stimulates hepatic glucose production. When the beta cell is not working, the glucagon-secreting alpha cell does not respond to hypoglycemia. Clearly insulin cannot be controlled by the body, so both aspects of regulation fail. Adrenaline still works, but some patients have responses delayed to a lower glucose level, lower than the onset of cognitive impairment.
- **Cognitive impairment sets in at below 2.8 mmol/L (50 mg/dL).** Confusion is followed by coma.
- Dr. Amiel presented some brain imaging studies on hypoglycemia awareness. In diabetic patients with hypoglycemia awareness, hypoglycemia produces a rise in cortical activation, whereas in patients with unawareness there is a drop in cortical activation.
- Loss of hypoglycemia awareness is more common the longer the duration of the disease; 25% of those who have had diabetes 15 years or longer are hypoglycemia unaware. Some forms of intensified insulin therapy are associated with loss of awareness.
- A 1991 study published by Heller et al. in *Diabetes* showed that loss of awareness is induced. After one day of hypoglycemia, counterregulatory responses on the second day were diminished compared with patients who did not experience any prior hypoglycemia.
- **According to Dr. Amiel, several factors make it difficult to avoid hypoglycemia:**
    - Non-physiological insulin replacement: "Insulin is a great drug, but it is not endogenous insulin. The pharmacodynamics do not match."
    - Loss of endogenous control of insulin and glucagon
    - Poor education on the actions/interactions of insulin
- Factors associated with recurrent severe hypoglycemia include loss of awareness, absence of fear of hypoglycemia, and fear of hyperglycemia.
- Providers are imprecise in telling patients how to adjust their insulin for exercise and alcohol. **In a survey of patients in the Emergency Room with severe hypoglycemia, 12% identify exercise as its cause, 19% alcohol, and 50% insufficient food.**
- **Dr. Amiel argued that we have to stop believing that good control and increased hypoglycemia risk are synonymous.** In her view, an assessment of control includes taking the amount of hypoglycemia into account.

- **#6: Sanofi-aventis symposium: Advances in Metabolic Control** *This session was chaired by Dr. Arya Sharma of McMaster University and took place over dinner at the Westin in Edmonton.*
    - **Dr. Hertzel Gerstein - Early Insulin Use in People with Type 2 Diabetes: Rationale and Clinical Experience**
    - Dr. Gerstein's goal was clearly stated: he believes we need to transition from insulin as a last resort to insulin as first-line therapy. We would quote from Dr. Gerstein's later debate over the merits of early insulin use: "Insulin is not holy water you sprinkle on someone before they die."
    - Also, echoing an idea we heard elsewhere at the conference, Dr. Gerstein said, "If you have diabetes, you don't have enough insulin. Despite this, and despite an absence of contraindications, physicians reserve it for late in treatment."

- Dr. Gerstein discussed the importance of good control, noting that in the UKPDS, a difference in A1C of 7.0 versus 7.9 led to a risk reduction of 12%.
- He summarized the new insulin delivery systems we have, naming pumps, aspart, lispro, glargine, and detemir.
- **The INSIGHT trial** was a Canadian-led trial of glargine in people with type 2 diabetes. In this randomized, controlled, prospective trial, people with type 2 diabetes were assigned to either oral medication or insulin. The data, which was originally presented at ADA, showed that those in the glargine group were 1.7 times more likely to achieve an A1C below 6.5% (from a baseline of 8%.) They also gave higher scores regarding their quality of life.
- In the trial, the patients who were on glargine were given a simple formula: for every morning that their fasting glucose was not below target, they increased their glargine dose by one unit. We believe that the superior results of the glargine are reflective of the fact that patients could titrate glargine more quickly than physicians could increase oral medication dosages. This is in fact an important argument in favor of glargine use.
- Relatedly, Dr. Gerstein attributed the higher quality of life scores—despite the injections—to an enhanced sense of self-efficacy in disease management.
- There were no differences in the rates of hypoglycemia, but there was more weight gain in the glargine group, with a BMI increase of 0.6 and a waist circumference increase of 2 cm.
- In Canada, there are apparently many plans that do not cover glargine insulin – amazing to us.

Dr. Stuart Ross
Therapeutic Management of Peripheral Health Risk in People with Type 2 Diabetes

- **Dr. Ross showed compelling statistics regarding MI** that were popular at the meeting: Steve Haffner has focused on cardiovascular complications, showing that a person who has diabetes and has never had a heart attack *has the same risk of heart attack* as someone who has already had one.
- Dr. Ross: "This is not just a disease of hyperglycemia—it's a disease of blood pressure and cholesterol."
- Central obesity suggests visceral fat, which we know is metabolically active and therefore more problematic than peripheral fat.
- Dr. Ross spoke to reasonable expectations that providers can have for their patients, such as suggesting a 5-10% weight loss as a goal. We know that this has a major metabolic benefit.
- **Dr. Ross emphasized that exercise prescriptions should be used**—not just a recommendation to exercise, but details on how often and for how long. His point was that providers should treat exercise as a therapy just as they treat drug intervention.
- Dr. Ross also highlighted rimonabant. He noted that it has multiple sites of action, and he reviewed the findings from RIO-Diabetes: A1C dropped by 0.7% overall, 0.3% of which was attributed to weight loss and 0.4% of which was believed to be independent of the weight loss.
- **In the Q&A,** someone inquired about the safety data on rimonabant. Dr. Ross responded that the safety data has been good, although there are some issues related to depression.
- **Another question asked about the effect of rimonabant on body composition.** The response was that it is indeed fat loss, and not loss of muscle tissue, and that this has been validated in studies. One question asked about the advantage of rimonabant over sibutramine, and Dr. Ross pointed out that rimonabant has the advantage of both weight loss and glycemic control.

- **#7: Glaxo-Smith Kline symposium: The Role of Insulin Resistance in the Development and Progression of Type 2 Diabetes** *This symposium drew a huge crowd—organizers had to bring in more chairs, and even then there was barely standing room. Dr. Stuart Ross and CDE Diane Lawlor did an excellent job with this topic.*
  - **Dr. Stuart Ross - The Link between Diet, Exercise, and Insulin Resistance Reduction**
  - **Dr. Ross stressed that diabetes is a progressive disease** and that providers must recognize this and continue to add treatments as necessary. In addition, he argued that there is no reason to delay treatment of diabetes.
  - He highlighted the links between visceral fat/abdominal obesity, cardiovascular disease, and insulin resistance. He also advocated for increased linking of science to patient treatments, noting that it has taken the medical community twenty years to acknowledge that post-prandial glucose control might be important.

- **Dr. Ross discussed Dr. Matthew Riddle's work on the dose-response curve.** This research found that at the highest dosage of medications, incremental increases lead to small improvements in A1C and large increases in side effects. Thus, we now know that it is better to use a combination of medications at 85% of their maximum dosage. According to Canadian guidelines, metformin is the first-line therapy, followed by the addition of TZDs.
- A survey of diabetes patients showed that 51% of patients are currently using lifestyle modifications or one oral agent only, while 6% use insulin alone, and another 5% use a combination of oral agents and insulin.
- Rosiglitazone has the effect of altering fat distribution: fat is moved from a central location up the periphery where it is no longer metabolically active.
- In general, Dr. Ross was firm that providers need to be doing more, sooner, and he cited the recently released Canadian DICE study in support of this. This chart-audit of 2.473 patients with type 2 diabetes found that 49% of patients are in poor control.

- **#8: Debate: Early Use of Insulin in Type 2** *Dr. Hertzel Gerstein (McMaster University) debated Dr. Jean-Louis Chiasson (University of Montreal) regarding the use of insulin as a first-line therapy for type 2 diabetes. This session was also very crowded, and the audience was highly engaged. The debate was judged according to how many members changed their minds as a result of the debate. Initially, the majority of the audience was in favor of early use of insulin in type 2, but Dr. Chiasson managed to persuade more people to change their minds and won the debate. Both speakers gave excellent and compelling presentations.*
  - **Pro: Dr. Hertzel Gerstein**
  - Dr. Gerstein repeated his argument that "diabetes develops when there is not enough insulin to maintain normoglycemia." As a result, he suggested, insulin was the most direct way to correct this problem. His presentation here was similar to his presentation at the sanofi-aventis-sponsored symposium in which he advocated for early use of insulin in people with type 2 diabetes.
  - In common between all the current therapies of type 2, he suggested, "insulin is the way all things ultimately work…In the end, insulin is the final common pathway."
  - Dr. Gerstein provided his "top 15" reasons to use insulin:
    - #15. There is no minimum or maximum dose.
    - #14. Providing insulin is replacing what's missing.
    - #13. Insulin is natural.
    - #12. Insulin is safe, even when used in people without diabetes, as was done in DPT-1.
    - #11. Insulin as first line therapy reduced outcomes in the UKPDS and Kumamoto studies.
    - #10. There are no contraindications of insulin and only one side effect.
    - #9. Insulin is titratable.
    - #8. Insulin can be mixed (ed. note – not all)
    - #7. Insulin can be mixed with other therapies.
    - #6. Insulin is easy to use (ed note – debatable!).
    - #5. "Even a cardiologist can do it (and they will have to learn how)!"
    - #4. It's painless—it just slips under the skin (ed note – many patients would object).
    - #3. It is only needed once daily (ed note - basal insulin only).
    - #2. We have more experience with insulin than almost any drug available.
    - #1. Insulin therapy was discovered in Canada!
  - In terms of trial evidence for early insulin use versus oral agents, Dr. Gerstein restated the results of the INSIGHT trial. In a comparison of glargine and oral agents, glargine patients almost twice as likely to achieve A1C targets while giving high quality of life scores.
  - Dr. Gerstein identified the main obstacles to early insulin use:
    - Messaging that the use of insulin is connected to a failure or a worsening of diabetes.
    - Messaging that the use of insulin means "I really do have diabetes."
    - Marketing: Why use insulin when you can use ….
    - Provider anxiety/lack of time/ignorance about insulin.
    - Provider threats to use 'the needle.'
    - Visual/cognitive impairment barriers.
    - Fear of pain and fear of weight gain.

- **Con: Dr. Jean-Louis Chiasson**
- The three basic elements of Dr. Chiasson's argument were 1) insulin does not protect the heart; 2) insulin does not preserve the beta cell; and 3) insulin is not without side effects.
- In UKPDS, insulin therapy did not offer any benefit over sulfonylureas.
- In the Kumamoto study, the power was insufficient to yield a statistically significant answer to the question.
- In the Digami study, there was no support for the claim that acutely introduced, long-term insulin treatment improves survival in type 2 diabetic patients following MI, but it did show that glucose control is important regardless of the method used to achieve this.
- Dr. Chiasson pointed out that the argument for insulin as "natural" is not accurate in the case of insulin analogs.
- Dr. Chiasson also argued that it is dangerous to underestimate the impact of hypoglycemia.
- Insulin therapy increases weight, and weight gain is associated with an increased risk of CVD.
- Insulin therapy also may be associated with increased risk for colorectal cancer.
- Treating to target remains the crucial goal.

- Q&A
- One questioner pointed out that the route of insulin administration is completely unphysiological.
- Another suggested that a pharmacoeconomic analysis should have been made and argued that insulin is more expensive than TZDs in the short-term.

--by Erin M. Kane and Kelly L. Close

6. **An In Depth Look at Novo's 2006** – Full Speed Ahead: Novo Storms through Canadian Diabetes Association!

Novo Nordisk took the Canadian Diabetes Association's annual meeting in Edmonton this month by storm, aggressively promoting its rapid-acting insulin aspart (Novolog, NovoRapid in Canada) and announcing that their long-acting insulin detemir will be available in Canada in January 2006.

The Canadian regulatory body approved Detemir, brand-name Levemir, six months earlier than anticipated. Novo Nordisk Canada President Patrick Loustau made the announcement in an elaborate "unveiling" in the CDA exhibition hall, culminating a morning that included a product theater presentation showcasing the rapid-acting insulin aspart – Novolog/NovoRapid - and iPod give-aways. Particularly in more insulin-centric Canada, this prompted some substantial excitement.

"We are well positioned to provide a solution for every patient that needs insulin," said Dr. Alan Moses, Associate Vice President of Clinical Research and Medical Affairs at Novo Nordisk, in a recent interview with DCU. "We have the whole spectrum, which is exciting from the standpoint of helping health care providers and patients." Novo's Levemir is poised to compete with sanofi-aventis's enormously successful long-acting insulin glargine, Lantus. In the Canadian market, Levemir will be available in pen form and will not be sold as a vial; according to Novo Canada Associate Director for Diabetes Marketing Tim Slee, the U.S. market is the only market in the world where vial use is remaining stable. In the U.S., Levemir was approved by the FDA in June and is expected to be available for both pen and vial delivery in first half of 2006. It is already available in more than 10 European countries and growth has been extremely impressive – in the third quarter, sales of insulin analogs reached 258 Euros, up nearly 60% versus a year earlier. Clearly with the North American markets yet to launch, Novo is set for robust growth on the insulin front, even if the human insulin franchises across the industry experience more moderate growth.

In Canada, detemir was characterized as a once-daily insulin, although in the US, it is labeled for one or two injections per day. In clinical trials, the long-acting insulins appear to have similar effects on glycemic control, and neither Levemir nor Lantus is meant to be mixed with other insulins due to potential effects on the absorption profile of rapid acting insulin in the mix (Levemir) or actual different pH levels (Lantus).

In differentiating its product, Novo highlighted both its effect on weight gain and its reduced absorption variability. All insulins currently available are associated with weight gain, but in clinical trials of detemir, the weight gain appeared to be significantly less than that for patients on NPH or glargine. In these trials, there was no weight gain

for type 1 patients and less weight gain for type 2 patients than was seen in trials of glargine and NPH. Unfortunately, we haven't yet seen a head-to-head study of Lantus versus Levemir. In a 12-week treat-to-target study published by Riddle et al. in *Diabetes Care*, the group of patients on NPH and the group of patients on glargine both gained an average of approximately 3 kg (6.6 lbs). A 12-week treat-to-target study of NPH versus detemir has been done; although the results have not yet been published, the weight gain is reported to be only 1 kg with Levemir. In a 24-week study of NPH versus detemir, the detemir group gained an average of 1.2 kg (2.6 lbs), compared with 2.8 kg (6 lbs) in the NPH group.

At the CDA, we learned that Levemir works differently from Lantus in that it binds to albumin in the body (albumin is a protein manufactured by the liver that is common throughout the body). Novo credits this binding system with the decreased variability of detemir, which has been shown in clinical trials; a 2004 clamp study published in *Diabetes* found significantly less within-subject variation than both NPH insulin and insulin glargine. Studies have also shown a lower risk of hypoglycemia when compared with NPH for both type 1 and type 2 patients.

Investigators are currently investigating possible reasons for the absence of weight gain with detemir, focusing on two possible hypotheses. First, investigators hypothesize that the albumin-bound insulin may circulate more thoroughly through the entire body and thus inhibit hepatic glucose production. Secondly, investigators speculate that there may be increased movement of insulin across the blood-brain barrier enhancing satiety signals, thereby causing weight loss via a central mechanism. Exogenous as well as endogenous insulin moves through the blood-brain barrier using a facilitated transport mechanism. To date, there is no published evidence in support of either one of these theories, though our eyes are pealed!

As Moses implied, the introduction of Levemir will make Novo the first company to offer a full portfolio of insulins, meaning that patients could purchase all Novo insulin, regardless of whether they were a type 1 patient on multiple daily injections, a type 1 patient on a pump, or a type 2 patient on prandial or basal insulin. Novo has been waiting for this for a long time; the company received an approvable letter in 2003 (see DCU #20), prompting a two-year delay, based on the FDA's request for more data on type 2 patients taking oral agents and more data in a broader, more ethnically diverse population. Although Sanofi-aventis *has* completed its insulin analog portfolio as well, they have delayed marketing their rapid-acting insulin glulisine, Apidra until it can be made available in pen form, which will apparently happen in the coming few months.

The complete portfolio of rapid-acting and long-acting insulin could make Novo more attractive to patients on both basal and bolus insulin; Novo is also targeting the pump market, promoting its short-acting insulin as better-suited to pump use over insulin lispro, Lilly's Humalog. At CDA, Dr. Simon Lawton, Novo Nordisk International Medical Manager, presented on short-acting insulins and their compatibility with insulin pumps. The presentation included data from a crossover study showing that insulin aspart had better local tolerability. Patients in the study experienced less pain, burning, inflammation, skin redness, and catheter occlusions with insulin aspart than they did with insulin lispro. Dr. Lawton also stressed insulin aspart's lower isoelectric point (5.1 for aspart v. 5.65 for lispro), noting that pH can drop at infusion sites in the presence of inflammation. At the isoelectric point, insulin can precipitate, causing problems with infusion.

Interestingly, Levemir is being launched just as there is *another* class that has been recently introduced – incretin mimetics – that both adds to the argument for earlier, more aggressive therapy. While Byetta, the only approved incretin mimetic, is labeled only for those *not* achieving goal with oral drugs, we understand at least some patients are trying on trying to back off insulin use, if various blogs are to be trusted! In terms of data - two-year open label data for Byetta at 104 weeks presented at ADA last June showed sustained A1C reduction and increased weight loss – while there has been talk of beta cell regeneration in animal models, we suspect it would take four or five-year data showing sustained A1C reductions before beta cell regeneration were accepted and insulin use as a rule would be put off more indefinitely. Still – if patients continue to do well on Byetta, they certainly won't look to move to insulin as quickly as they otherwise might have and likely won't be pushed *toward* insulin either.

Not that PCPs appear to be doing *that* much pushing anyway, relatively speaking… despite Lantus success, new CDC figures recently out show that from 2003 to 2005, insulin use by type 2 patients fell from 31% to 28% of the group (insulin only or combined with orals) – see more at http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf. Dr. Moses did emphasize that GLP-1 analogs won't do *away* with insulin, and of course he's right – there's room for a lot of therapies to win here, given the underlying theme of moving to more aggressive therapy sooner and given the

growth in the overall audience. We could see, of course, increased insulin use if combination therapy takes hold in the coming years, which we believe is likely to happen.

Novo itself may have the same belief – it has a GLP-1 in development, NN-2211, although it won't enter phase 3 until 2006, and we wouldn't look for it to reach "fast follower" status since it likely won't reach market much before 2009. Even though it has experienced delays, Novo appears quite committed to NN2211 – and why not, given all the safety issues with the other new classes!

Even considering that Byetta is a novel new attractive option, we believe that the launch of Levemir *will* make it easier for primary care physicians to continue to push earlier, more aggressive therapy broadly speaking – more Byetta, more insulin – more therapy, overall. Ultimately, do we think long acting insulin analog use will go *up* because there will be so much larger an audience progressing to insulin (and who are used to injections due to Byetta!?) or will go *down* because this group will delay the move to insulin? We would imagine that at least in the short run, people will move to basal insulin more slowly because there is another treatment in the armamentarium prior to insulin. To boot, we imagine some patients are backing off insulin, particularly if they are on a basal insulin only, even if the label doesn't support this. (Even if doctors aren't prescribing such treatment, patients often decide treatment on their own.) Longer term, long-acting analogs may just be added to Byetta and the rapid acting analogs may be the insulin that loses some steam.

We know that in hiring 400 additional sales force to cover PCPs in the US, Novo is aiming for similar success that Lantus experienced - Lantus was launched in 2001 and after a first year of sales of approximately $50 million, sales grew to over $1.0 billion in 2004, representing one of the most successful launches ever of a diabetes drug. We certainly forecast success for Levemir, given the strength of Novo as a diabetes powerhouse, the strong base of Novolog, the new salesforce additions, and the benefits of Levemir versus Lantus.

Indeed, Dr. Moses emphasized Novo's belief that current therapy is inadequate to achieve the goals that have clearly shown to reduce complications of diabetes. He characterized the launch of Levemir as the final component of a package that could dramatically improve patient outcomes. "Our goal is to create a therapy that patients can use - to provide a package with the right insulin, delivery system, and education."

--by Erin M. Kane and Kelly L. Close

7. **Clinical Literature Reviews:**

- ***JAMA* Early Release Alert! "*Effect of Muraglitazar on Death and Major Adverse CVD Events in Patients With Type 2 Diabetes Mellitus*" ~ "*Selling Safety--Lessons From Muraglitazar*"** We try to watch clinical literature closely as it often has important implications for industry. This was never more true than with a recent piece in *JAMA*, written by powerhouse cardiologist Dr. Steven Nissen, et al. We mean – one day, there was a panel meeting for muraglitizar, with no one seeming all that focused but the compound seemingly headed, if uneasily, for approval – the next day, Nissen and Cleveland Clinic colleagues have done a rock-star analysis of the data, turning up many disturbing facts and trends:
- The authors point out that they got nearly all their data from the FDA website – it makes one wonder what the panelists were reading? We have all the respect in the world for FDA panelists but also believe the FDA isn't leveraging the best experience it could in panelists it invites for these meetings. In an effort to stay away from anything remotely resembling bias, the FDA appears to appoint panelists who have no experience with drugs in question. We get the bias question and why it's tough, but wouldn't you want to benefit from experience? And wouldn't the people best for the job be people who know something about the drugs in question? The fact that this is all publicly available info also actually reminds us just how difficult it is to get clinical trial data unless the companies are forced to give for panel meetings and even when one can lay hands on data, how often difficult it is to get full data sets, adverse events and all.
- The authors added CHF and TIA to the all-cause mortality and got 2.11% incidence for treated group vs. 0.81% for placebo. Adjudicated CHF (confirmed by signs, symptoms, clinical tests, etc.) was 13/2374 for muraglitizar (0.55%) and 1/1351 controls (0.07%). That was only "nearly significant" - though apparently significant for the dozen extra in the muraglitizar group, yes? The RR for CHF was much higher in the reconstituted data group - the authors god rid of the low dose group (2.5 mg – why would you keep this if it wasn't to be used in real life) and re-did the numbers, which provided very convincing results that really, all else equal, why would one even consider taking this drug?

- To boot, they point out the although patients with mild CHF were recruited, only 25 were included - BMS says that safety was demonstrated for this group, which the editorial characterizes (appropriately, in our view, what else can one say?) as a hollow assertion.
- The authors are fairly dismissive of muraglitizar early in the commentary: "...Development of dual - PPAR agents has been considered a highly promising strategy for simultaneous treatment of both hyperglycemia and dyslipidemia in diabetic patients. The first of these agents to be considered for FDA approval is muraglitazar, which can be characterized as a strong PPAR-gamma agonist with moderate alpha effects."
- It gets worse! (How could it not?) "With any new class of pharmaceutical agents, unexpected toxicity may emerge during the development program. However, in some cases, pharmaceutical sponsors defer or withhold publication of phase 2 and 3 clinical trial data until after drug approval. Accordingly, documents submitted to the FDA for consideration of approval may constitute the only publicly available source of objective information for newly approved pharmaceutical agents. This has been the case for muraglitazar for which the public disclosure of phase 2 and 3 data occurred via the FDA web site shortly before the advisory panel convened to consider the drug for approval on September 9, 2005." They go on to discuss the adverse event analysis of the data that they did, which they characterize as "concerning." They go on to show the risk ratio for CVD events associated with mura to be high - and they note that "...Moreover, patients who are enrolled in clinical trials often constitute the lowest-risk strata of patients, and the real world exposure would likely substantially amplify the risk. Taken as a whole, these data demonstrate that it is likely that muraglitazar, if approved by the FDA, would constitute an unacceptable patient hazard."
- They go on to criticize the composite endpoint - controversial in this trial design (not including edema and CHF, since they are known hazards of PPAR gamma).
- Importantly, they point out that each PPAR activates or suppresses different genes with only partial overlap in activity - so each agent has to be considered separately in terms of efficacy and safety.
- The conclusion is that muraglitizar shouldn't be approved. And of course, what happened, but the FDA days later sent BMS an approvable letter. "The estimated magnitude of this risk (mortality and morbidity) is substantial with RRs indicating a doubling for irrevocable, major end points and composite outcomes. The consistency of these RRs suggests that this result is not due to chance. Accordingly, muraglitizar should not be used or approved to treat patients until an appropriate dedicated trial to assess cardiovascular outcomes is performed."
- Now, there are approvable letters and there are approvable letters. The first reference to this letter made by BMS seemed a half-hearted attempt to suggest new trials wouldn't be necessary – the second reference made by BMS seemed to imply not only new data, but new outcomes studies would be needed. Go figure. We note, by the way – FDA studies today just aren't powered for safety and it's right, but very difficult to make that so. You can get patients to do randomized trials, for example, for a year, but they get (or suspect) placebo, and forget it, a 5-year trial? We're not saying it can't be done, but the enrollment complications are non-trivial.
- So what next - what will the FDA do? Can't imagine after this they will go for "observational post-marketing" surveillance. As the commentary "Selling Safety – Lessons from Muraglitizar" suggests (it's very well done by the way and full text is available at http://jama.ama-assn.org/cgi/content/full/294.20.jed50074v1?etoc), this "meticulous examination" of data by Nissen would be likely to slow down any drug apparently destined incorrectly for approval.
- We wrote earlier this month in notes to clients that we believed this may have an impact on inhaled insulin approval. It was interesting in that FDA panel meeting that Dr. Orloff just seemed to start off the whole meeting with the view that the FDA needed to create more options for patients. Whether or not this option is one created – and we think it probably will be – the safety concerns surrounding our therapeutic area right now would probably slow down any new treatments.
- With that in mind, we've been struck for some time now how Amylin keeps benefiting from competitor woes like the current *JAMA*/muraglitazar calamity. Let's think – so first there were all the issues with the dual PPARs a couple of summers back, when the FDA made them all return to do two-year cancer toxicity studies. BMS/Merck was the only one that apparently had these studies done, though as happens with the FDA, thinking evolves, minds are changed, and more learnings come to the fore – BMS didn't benefit from that, after all! We'll be back to this in a minute. Then, Conjuchem woes started and really didn't stop and they still probably haven't stopped. Then Novo delayed Liraglutide by about a year last October. Then Novartis problems (non-inferiority, etc – see September blog) with LAF-237 happened, then, muraglitazaar's problems at ADA, where the compound just really couldn't get any real traction. And remember – although GLP-1 is a new class, a panel meeting wasn't even required for Byetta! The drug is getting a bigger and bigger area all to itself, it seems.

- ***NEJM*: "*FDA Standards – Good Enough for Government Work*?" –** So this perspective, written by Harvard epidemiologist Jerry Avorn, MD, was excellent. This editorial came out slightly after Labor Day and made us nod vigorously. It's all about how sloppiness at FDA "*resides not in the quality of execution the FDA requires, which is high, but in the questions it asks*…" That's too reductive, of course, too easy, but perspective makes it less so. Notably, by the way, there are negative references in and between the lines on Sanofi's Acomplia.

--by Kelly L. Close

8. Quick Takes

Funding: We're going to be writing a more in-depth story on this one of the next times around but check it out – there are a lot of companies being funded right now.

- Alinea (biopharmaceutical) just closed a $45 million series A;
- Optiscan (monitoring) closed $36 million in new financing;
- Veralight (screening) closed $5 million in a series A;
- Diakine is in the midst of discussions, as are many other companies – it will be extremely interesting as always to watch.

New CDC Stats: These came out, finally. A couple of things to highlight from the details on the blog: 1) There are now 20.8 estimated patients, up from 18.2 – there are estimated to 14.6 million diagnosed patients, which represents growth of 12% - so that's bad – but there are now estimated to be 6.2 million undiagnosed, up from 5.0 million in 2003, up 24%. Yes, lower base, etc – but still, that says something about the extraordinarily needs on the screening front. As far as meds go, 57% are now estimated to take oral agents, up from 54% in 2003, and those on insulin only have declined to 16% of patients from 19%. Combination therapy has remained constant. So although insulin companies are certainly benefiting from a higher number of patients, they aren't necessarily succeeding in changing behavior according to this data. Next time around, we'll be interested to see how the CDC counts people benefiting from the sea change ongoing for patients going on incretins ~

9. Earnings Glimpses – We've put all our earnings discussions on our blog this time – see www.diabetescloseup.com for our thoughts on business at Abbott, Amylin, BMS, J&J, Novo …by and large, we see blood glucose monitoring growth settling in above 10%, pump growth stable at over 20%, and drug growth either very strong, relative to expectations (Lantus, Levemir, Symlin) or very weak, depending on what you've got. Pipeline news is quiet or negative. We loved hearing the Amylin would do a special trial for type 2 patients on basal insulin who would take a dose of Symlin before each meal. Why? We're pretty sure this patient cohort will do well on Symlin and having more published data for the PCPs is always a great thing. We get the sense Symlin sales are healthily above expectations, and it's only the start, of course. Symlin is going to be a great prandial drug for PCPs to use – say that patients have some prandial needs – well, if they take Symlin without insulin, they won't be at risk for hypoglycemia (assuming correct Lantus/Levemir dosing), their post-prandial numbers will likely improve nicely, and they stave off mealtime insulin.

10. Conference previews – Diabetes Technology Society, Levine Symposium – Advances in Diabetes Research, AHA, ADA Postgrad, Continuous Monitoring/Insulin Delivery Meeting

- **The Diabetes Technology Society** meeting takes place in our fair city by the bay (www.diabetestechnology.org) November 10–12. The speaker line-up is most impressive and we couldn't hope to do justice here, but it includes, Steve Gutman, MD of the FDA on continuous monitoring, Anthony Furnary, MD, on continuous in hospital ICUs, fantastic industry leaders, too many to list, on various new technologies, Robert Lustig MD on pharmacological approaches to obesity, Theodore Ciaraldi, MD on ECBs and rimonabant, Bob Sherwin, MD on hypoglycemia, Matt Riddle, MD on insulin treatment, Irl Hirsch, MD on interactive diabetes management, and last but not least, the fabulous survey at the end, which will include Bruce Buckingham, MC, Aaron Vinik, MD, Dorian Liepmann, PhD, and Jan Wojcicki, PhD. To *boot*, Ross Jaffe, MD, of Versant Ventures and I are co-organizing a workshop on the "Business of Diabetes" – what should be some terrific discussions on glucose monitoring, insulin delivery, pharma, and stem cells. We have a slew of outstanding panelists and look forward to an engaging set of discussions. We hope to see you there ~!
- **6th Annual Rachmiel Levine Diabetes and Obesity Symposium:** This happens almost the very same time as DT&T – November 9-12 in LA. We always learn enormously at this meeting and this should be no exception. We look forward, in particular, to David Cummings, MD on gastric bypass surgery and Brian P Kennedy, PhD on PTP1Bs, Jerrold Olefsky, MD, on the role of inflammation, Paul Robertson, MD on

oxidative stress and glucose toxicity, David Harland, MD on endogenous pancreatic insulin production restoration in type 1 patients, Garry Steil, PhD, on closed loop insulin delivery, Michael German, MD on gene expression cascades, Lawrence Rosenberg, MD PhD on the role of INGAP in islet cell neogenesis, Susan Bonner-Weir, PhD on the role of pancreatic progenitors in islet expansion, Lucienne Chatenous on anti-CD3, Bernard Hering MD on immunobiology of islet transplantation, Camillo Ricordi on new islet transplantation trials, and Dick Insel, MD, on the role of the JDRF in islet transplantation.

- **AHA –** This takes place in Dallas November 13-16. Oh, no one told you this was a diabetes meeting? It is. There are ten symposia alone on diabetes over twenty key sessions on diabetes, obesity, and metabolic syndrome, and one super-key late breaker (Monday, 10:45 – 12), FIELD (check our blog this week, we'll be writing up a report on why this promises to be such an important session).
- **ADA Postgrad** – Yes! It's back in our city by the bay, taking place February 10-12. We would go just to hear Aaron Vinik, MD on neuropathy, and we'd also go just to hear Daniel Drucker, MD on incretins, and we'd also just go to hear Trevor Orchard, MD on glycemic control and CVD risk, and we'd also go just to hear Virginia Valentine, CDE on pump use and special health considerations, and we'd also go just to hear Henry Ginsberg, MD, on dyslipidemia treatment, and we'd also go just to hear Bill Polonsky, PhD on behavior change implementation, and we'd definitely also go just to hear David Kendall, MD on new drug therapies in diabetes, and we'd also go just to hear John Buse, MD, PhD, on cardio-metabolic risk, and ..
- **2nd Annual Clinical Diabetes Meeting** – this is the second annual meeting focusing on continuous monitoring and insulin delivery – it will be held in Boston, April 21-22, 2006.
- **49th Scientific Annual Meeting of the Japan Diabetes Society** takes place in Japan, Tokyo May 25-27, 2006. http://www2.convention.co.jp/jds49/english/greetings/index.html

--by Kelly L. Close