Follow-up based on stratified risk is recommended:

Risk Category	Follow-up
0	Annual review
1 (LOPS ± deformity)	3-6 months
2 (LOPS ± PAD)	2-3 months
3 (pervious ulcer or amputation)	1-2 months by a specialist

(Boulton. *Diabetes Care* 2008)

Finally, Dr. Boulton highlighted several recent studies that have investigated inflammation as a precursor to ulceration and heat as a signature of the presence of inflammation (Lavery et al. *Diabetes Care* 2007; Armstrong et al. *Am J Med* 2007). These investigations show that an increase in foot temperature correlates to more than a 3-fold increase in the risk of ulceration. Several instruments are now available that can be used by the patient for self-monitoring of foot temperature, including the handheld TempTouch® and TempStat, a liquid crystal pad that the patient stands on.

Pancreatic Stem Cell Therapy: A Big Step Closer to Reality

Results from recent *in vivo* studies suggest that transplanted islet cells that are derived from human embryonic stem cells (hESCs) can provide stable, lasting glucose control. In a session titled, "New Hopes for Stem Cells," Emmanuel Baetge, PhD, Chief Science Officer, Novocell, San Diego, CA, discussed not only the efficacy of such an approach but also the means to sustain the transplant without suppressing the patient's immune system.

The International Diabetes Federation estimates that there are over 246 million patients who are currently diagnosed with either type 1 or type 2 diabetes, a figure that is expected to balloon to 380 million cases by the year 2030. To date, the treatment of diabetes has been the straightforward maintenance of blood glucose homeostasis by the direct administration of insulin or by other pharmacologic means. However, such interventions do not address the underlying problem of dysfunctional pancreatic islet beta-cells and imperfectly controlled blood glucose levels. The ideal solution, therefore, is long-term islet cell protection or, failing this, islet replacement.

"Type 1 and 2 diabetes is a beta-cell mass disease," said Dr. Baetge. "The question for replacement is can we substitute primary islets with something that comes from a stem cell?" Driving this question is the fact that primary islets, such as the source that was used in the Edmonton Protocol, are harvested from human donors; this approach requires life-long immune suppression for the recipient, and the cell source is not amenable to scale-up.

Directed Differentiation

The use of hESCs in this, or any, setting is predicated on the ability to produce the type of cell that is required, and for Dr. Baetge, this entailed the "recapitulation of embryonic development required for pancreatic islet cell formation." In order to drive the *tabula rasa?* hESC to eventual beta-cell production, the first step is differentiation into the definitive endoderm, the progenitor of the pancreas and liver, among other cell types. The ability to do this with hESCs was first demonstrated by the Novocell team in 2005 (D'Amour et al. *Nature Biotechnology* 2005).

Shortly following this, the methods of differentiation to produce pancreatic endoderm and then pancreatic endocrine cells were established (D'Amour et al. *Nature Biotechnology* 2006); the therapeutic function of these cells was demonstrated in April of this year (Kroon et al. *Nature Biotechnology 2008*). In this study, mice were first implanted with the pancreatic islet progenitor cells that gave rise to glucose-responsive human C peptide-secreting islet cells over 60 to 90 days. The animals were then exposed to streptozotocin, an agent that is selectively toxic to rodent but not human insulin-producing islet cells. The STZ-treated animals remained nondiabetic after STZ destruction of the endogenous mouse beta-cells. Using C-peptide as a surrogate marker for insulin, as well as blood glucose levels, researchers showed that the implant was able to maintain glucose homeostatis, and further, islet grafts that were maintained out to 120 days exhibited all the properties of functional beta-cells. "The development of these cells *in vivo* is replicating what you'd expect in normal biology," said Dr. Baetage. Glucose control was lost when the implant was removed.

As this approach comes closer to clinical implementation, 2 issues still require resolution—first, the enrichment of cell product for the desired cell type (regardless of the method, other cell types will inevitably be present, which are allowed as long as they are safe), and second, protecting the implant against the patient's immune system. For purity, optimized differentiation and enrichment strategies can achieve a progenitor cell population that is greater than 80% enriched. For stable delivery without immunosuppression, Novocell currently is evaluating its own polyethylene glycol hydrogel coating system in addition to other retrievable encapsulation systems. Successful encapsulation requires good biocompatibility for subcutaneous placement, protection of implanted cells from immune rejection, and facilitation of the appropriate vascularization for maintenance of islet cell function and health.