Part Human, Part Machine: The Artificial Pancreas Automates Insulin Therapy for Type 1 Diabetics

Brian McGarry

Writer's Comment: *There are no breaks from diabetes. From the moment of diagnosis, managing Type 1 diabetes is a twenty-four hours a day, seven days a week task. Failure to consistently keep blood sugar within a normal range puts a diabetic at risk of chronic health problems. My interest in diabetes led me to get involved with the Diabetes Advocacy and Awareness Group, a group of student volunteers at UC Davis. With this group, I started attending "Type 1 Talks," a support group for Type 1 diabetics on campus and in the community. I was fascinated by stories shared by members of the group that detailed the daily challenges of managing diabetes. In one of the sessions, an invited guest speaker started a discussion about emerging research and technologies in diabetes care. One such technology was the artificial pancreas. I left the session with only a basic conceptual understanding of the technology, but it showed great promise to lessen the burden of managing Type 1 diabetes. The task of writing a Science Article for Dr. Karma Waltonen's UWP 104F was the perfect outlet for me to investigate this technology in greater depth and share my findings. Thanks to Dr. Karma Waltonen for her guidance through the writing process. I would also like to express my deepest gratitude to the members of the Diabetes Advocacy and Awareness Group and the members of "Type 1 Talks" for sharing their experiences and welcoming me into the group.*

Instructor's Comment: *Rarely do students immediately know what they're going to write their first paper on in UWP 104F: Writing in the Health Sciences. Brian entered the class with a determination to succeed, to improve his writing, and to explore the artificial pancreas. His fascination with the subject led to several written iterations—a science article and a grant proposal among them—and a wonderful presentation to an engaged class. Brian demonstrates here all the qualities of a strong scientific article written for an educated, but non-specialized audience—an ability to clearly relate complex scientific ideas, to construct a readable piece from many disparate parts, and to bring a narrow subject alive for a broad readership.*

—Karma Waltonen, University Writing Program

Day to day, a Type 1 diabetic does everything you and I do but with the added responsibility of multiple blood draws and injections. These individuals are less efficient at accessing the energy stored in food and require injections of the hormone insulin to stay alive. A Type 1 diabetic invests a great deal of time and energy into this as not doing so puts her at risk of serious health complications and even death. The artificial pancreas aims to lessen the burden of Type 1 diabetes by automating the process of insulin injection. The device limits the time a diabetic patient must spend calculating proper insulin doses and provides better blood sugar regulation than can be achieved with current technologies, reducing the risk of diabetes related complications.

Nestled just beneath the stomach is the pancreas. This peculiar organ is dually employed with both exocrine and endocrine responsibilities. In addition to producing enzyme-laden juices it excretes into the small intestine to aid in digestion, the pancreas specializes in making a series of hormones it releases into the blood stream. Hormones, the functional components of the endocrine system, are small endogenous molecules that act as signals over long or short distances and regulate body function. Insulin is a pancreatic hormone facilitating the uptake of the basic energy unit glucose from the blood stream into cells where it can be burned for energy. When an individual's immune system destroys β-cells in the pancreas—those responsible for producing insulin—the amount of insulin in the blood can fall dangerously low. Consequently, the body is unable to effectively regulate blood sugar levels and access the energy stored in glucose. This metabolic abnormality is known as Type 1 diabetes mellitus.

When cells take up insufficient amounts of glucose from the blood plasma, blood sugar is raised above normal and hyperglycemia ensues. In the kidneys, which filter waste and reabsorb vital blood components, glucose concentration can be so high that it exceeds the kidneys' capacity to reabsorb it. As a result, glucose enters the urine. This creates a concentration difference that also pulls water into the urine. This effect is responsible for two common signs of diabetes, polyuria (excessive urination) and polydipsia (excessive thirst) (JDRF "Diabetes"). In fact, the name diabetes mellitus, meaning "a siphon" and "sweetened with honey" (Oxford English Dictionary "Diabetes" "Mellitus"), is a vestige of the archaic practice by which a physician diagnosed the disease "based on the taste of the [patient's] urine" (Gale 3353).

Although these symptoms seem trivial, Type 1 diabetics face a host of serious health risks. The role of insulin in metabolism is crucial as its "regulation…determines the balance between synthesis and destruction of tissue substances" (Burgoyne 1514). Insulin deficiency results in complex metabolic pathologies that can lead to "increased appetite" and "sudden weight loss" (JDRF "Diabetes"). Another significant complication of Type 1 diabetes is ketoacidosis. In *Emergency Nurse,* Val Wilson reports that "diabetic ketoacidosis is the most common cause of mortality in people with Type 1 diabetes under the age of forty" (Wilson 14). Daniel Foster and J. Denis McGarry of The University of Texas Health Science Center explain that when there is an insufficient amount of insulin in the blood, a series of changes in several metabolic pathways occurs. The body is thrown into a "catabolic state," favoring breakdown over synthesis. Pathways that break down fatty acids are stimulated, and "ketone bodies" are generated as a byproduct. These ketone bodies alter the acidity of the blood and body tissues and cause the brain to swell, often resulting in death (Foster and McGarry 166).

Given the acute physiological dangers of Type 1 diabetes, the availability of therapeutic insulin is crucial for the care of diabetic patients. In an article in *Perspectives in Diabetes*, Edwin Gale suggests, "insulin changed childhood diabetes from a rare fatal disease to a condition in which prolonged survival was possible" (Gale 3354). Insulin therapy is so paramount to managing Type 1 diabetes that the disease is often interchangeably referred to as insulin dependent diabetes. Although access to exogenous insulin has given life to sufferers of Type 1 diabetes, it is in no way a cure (JDRF "Type 1"). When the body does not regulate blood sugar, this responsibility falls on the individual. This requires a diligent regimen of multiple daily blood sugar checks and insulin doses.

Management of diabetes with insulin therapy does not, however, eliminate the risks associated with the disease. Given the sensitive and precise hormonal control of blood sugar in the body, it is easy to imagine how managing diabetes with insulin therapy is less like flipping an on-off switch and more like pressing a sensitive gas pedal. Too much insulin and blood sugar can drop dangerously low. Too little and diabetic ketoacidosis can result. The goal is to keep blood sugar within a normal range. Further complicating the task of managing blood sugar is the reality that stress, both physical and emotional, affects the way the body regulates blood sugar (UCSF). The diabetic must adapt to the

nuanced impact of different foods, stresses, and exercise on her blood sugar and adjust insulin dosage accordingly. Indeed, managing Type 1 diabetes is a highly skilled task. Failure to consistently keep blood sugar within a normal range raises the risk of developing diabetes related complications. The Juvenile Diabetes Research Foundation reports that chronic hyperglycemia can "eventually damage blood vessels, nerves, and organ systems in the body" (JDRF "Diabetes").

In light of the challenges Type 1 diabetics face in managing blood sugar and the potential risks of poor management, many technologies have been developed to improve regulation. One such technology is the insulin pump, which periodically pumps doses of insulin through a resident subcutaneous needle throughout the day. The continuous glucose monitor provides frequent blood sugar values without blood draws. The National Diabetes Information Clearinghouse, a division of the National Institutes of Health, describes the continuous glucose monitor system as "a tiny sensor inserted under the skin to check glucose levels in tissue fluid" that "sends [this] information to a…wireless monitor" (NIDC). Providing more frequent, almost "real-time," measurements allows better regulation of blood sugar levels (NIDC). However, the device is limited by its inaccuracy. It must be calibrated by comparing the continuous readout to a standard blood glucometer, which requires a blood sample. In addition, standard readings must confirm the glucose levels indicated by the continuous meter before "making a change in treatment" (NIDC). Furthermore, the sensor must be replaced frequently (NIDC). Although a step towards improved control of blood sugar, the continuous glucose monitor must overcome these problems before it becomes widely available.

Considering the importance of adequate blood sugar regulation and the fact that "as many as three million" people live with Type 1 diabetes in the U.S., the demand for an artificial pancreas is high (JDRF "Type 1"). Although it sounds like science fiction, the artificial pancreas is, in theory, quite simple. The Food and Drug Administration reports that an Artificial Pancreas Device System "automatically monitors blood glucose and provides appropriate insulin doses" (FDA). The goal is to develop a system that independently regulates blood sugar by controlling insulin input into the blood, the endocrine function of the pancreas. The FDA indicates that an artificial pancreas may be entirely mechanical, in which the "components might be external or implantable" (Pinkos et al. 26). It could also be "entirely biological, a mechanical-biological hybrid, or a

semi-closed system that involves actions by the patient" (Pinkos et al. 26). The artificial pancreas therefore represents not simply a single device, but a concept, a larger field of potential devices designed to mimic endocrine control of blood sugar. Many of the most thoroughly tested and promising artificial pancreases are of the mechanical variety and will be the focus of this discussion. Garry M. Steil, A.E. Panteleon, and Kerstin Rebrin explain that the mechanical system, "in addition to insulin," requires three things: "a pump, a glucose sensor, and an algorithm" (Steil, Panteleon, Rebrin 126). Arleen Pinkos et al. of the FDA indicate that, functionally, "a mechanical artificial pancreas consists of inputs… continuously fed to a controller where a mathematical algorithm applies a set of rules to generate an output" and "subsequent information from inputs would result in adjustments to output" (Pinkos et al. 26). While both insulin pumps and continuous glucose monitors are currently in use by Type 1 diabetics, they require user input. As previously mentioned, the patient processes the results of blood sugar checks and information about his or her activities and diet to decide on the best insulin dose to administer. However, completely automated blood sugar regulation requires an algorithm to "close the loop" (NIDC). The system is therefore a feedback loop that mimics the sensitive endocrine fluctuations involved in controlling blood sugar. The FDA establishes the "relevant endpoints for trials" of an artificial pancreas as "improvement of glycemic control with a reduction in hypoglycemia" (Pinkos et al. 27). With pump and continuous glucose sensing technologies on the market, the task becomes deriving an algorithm and integrating all of the parts into an efficient, working system.

What better way to derive an algorithm for insulin delivery than to model physiological insulin regulation in healthy people? In "Modeling β-Cell Insulin Secretion—Implications for Closed-Loop Glucose Homeostasis," Garry Steil et al. suggest, "a model that characterizes β-cell insulin secretion as a function of glucose might form the basis for an algorithm linking a glucose sensor to an insulin pump" (Steil et al. 953). By mirroring the normal response of the β-cell to changes in blood sugar, such an algorithm, when functionally connected to a sensor and pump, could keep blood sugar within a normal range. To chart the physiological insulin response, Steil et al. studied the responses of nondiabetic patients to elevated blood sugar. Intravenous catheters were used to maintain elevated blood sugar levels while blood samples were taken at regular intervals to

determine both glucose and insulin concentrations (Steil et al. 954). The researchers then compared the normal insulin response profiles to those predicted by several existing mathematical models. The group revealed that while both models demonstrated the ability to imitate pancreatic insulin secretion and "establish and maintain" normal blood sugar, the "physiologic insulin delivery (PID)" model in particular "result[ed] in a more stable closed-loop system" and exhibited "an innate ability to adapt to changes in insulin sensitivity [and] glucose appearance" (Steil et al. 954, 960). Given the PID model's ability to adapt to these subtle forces governing blood glucose fluctuation, it seems best suited to mimic pancreatic insulin secretion.

Just as it is unfair to expect a masterpiece from a novice painter, it is unrealistic to expect the PID model to capture all of the nuances of hormonal blood sugar regulation without further refinement. Steil, Panteleon, and Rebrin acknowledge, "the ability to recreate the β-cell… response with a secretion model does not…ensure that adequate control will be achieved during day-to-day use" (Steil, Panteleon, Rebrin 134). The reality of insulin and blood sugar dynamics is much more variable and complex than in a controlled experiment. It follows that functionality in a controlled setting does not prove efficacy in a real-life environment. Steil, Panteleon, and Rebrin suggest, "the model must ultimately be able to recreate the insulin secretory profile for meal and exercise profiles" (134). That is, it must be able to maintain "normoglycemia" when faced with daily stresses to blood sugar, including meals and exercise. These issues must be addressed before the closed-loop system can become a safe and feasible therapy option.

With recent advances in the basic technologies required for an artificial pancreas device, the actualization of the concept into a widely accessible system is close. Researchers have experimented with several different functional systems using combinations of subcutaneous, intravenous, and intraperitoneal (inside the body cavity) glucose sensors and insulin pumps. Each has come with benefits and limitations. Steil, Panteleon, and Rebrin report, "depending on the type of sensor and its location, different delays and noise will be present" and "depending on the type of pump and its location…the insulin dynamics will be different" (Steil, Panteleon, Rebrin 134). These differences provide unique challenges to improving the effectiveness of the artificial pancreas system. Eric Renard of Montpellier University and coworkers indicate that because of "delays

in insulin absorption and action and…blood glucose assessment," the subcutaneous sensor-subcutaneous pump method "result[s] in limited reactivity to glucose and insulin delivery changes" (Renard et al. S174). This problem reduces the ability of the "SC-SC approach" to keep blood glucose levels within normal ranges (S174). In a later publication, Renard explains that for the subcutaneous method of insulin infusion, "variability…is significantly reduced by fast-acting analogs" (Renard 736). Fast-acting insulin analogs such as "insulin lispro offer faster subcutaneous absorption [and] an earlier and greater insulin peak" (Noble, Johnston, and Walton 279). This helps combat the effect of delays in glucose monitoring and insulin activity. With its simple and accessible components, the subcutaneous monitor-subcutaneous pump system has the benefit of feasibility for everyday use outside of a hospital or clinic.

Compared to the subcutaneous monitor and pump system, an intravenous continuous glucose monitor used in conjunction with an intraperitoneal insulin pump has proven much more sensitive in regulating blood sugar. Eric Renard et al. explore this model and its ability to function as an artificial pancreas. The continuous glucose monitor is placed in a large vein near the heart and connected to an intraperitoneal insulin pump by a subcutaneous lead (Renard et al. S175). An external wireless controller using a PID algorithm calculates insulin doses and regulates the pump (S175). The greater sensitivity of this setup is due to the fact that "absorption using the intraperitoneal route is quicker [and] more reproducible" (S174). Renard et al. have shown the extreme efficacy of this system to capture pancreatic endocrine function. His group reports that the "effectiveness of intraperitoneal infusion from implanted pumps allows lower average [glucose] levels, reduced blood glucose variability and a dramatic decrease of severe hypoglycemic events" (S174). This system seems to actualize the end goals for the Artificial Pancreas Device System established by the FDA. However, it is not without its problems. During closed-loop control, fluctuation in blood glucose levels following meals presses the need for algorithm adjustments (S177). As such, this system will still likely require user input to better control blood sugar after meals, at least until the algorithm is refined (S177). Furthermore, due to the invasiveness of the pump and sensor, the system is limited to use in clinical settings.

Clinical trials have shown that a closed-loop system that mimics pancreatic insulin secretion is, in fact, achievable. However, a considerable

gap exists between trial systems and a safe and reliable market-worthy device. Bridging this gap requires advances in glucose sensing and insulin delivery technologies as well as refinements to secretion algorithms to improve sensitivity when challenged with variable stresses to blood glucose. With the potential to improve the lives of millions of Type 1 diabetics worldwide, efforts to develop an artificial pancreas device certainly seem worthwhile. However, with concurrent research being conducted to develop a cure for Type 1 diabetes, is the artificial pancreas a waste of time and money? Is it a distraction from the more significant possibility of a cure? After all, the artificial pancreas is only a therapy, one that mitigates but does not reverse the aberrant physiology present in Type 1 diabetics. While the Juvenile Diabetes Research Foundation "remains dedicated to finding a cure," it acknowledges that this search is "a marathon effort, not a 'sprint'" (JDRF "Leadership"). With the possibility of a cure hanging in the distance, the artificial pancreas promises to improve the lives of millions of people suffering from Type 1 diabetes.

Works Cited

Burgoyne, Frederick H. "The Pathology of Diabetes Mellitus." *The Canadian Medical Association Journal* 84 (1961): 1415-1417. Web. 29 Jan. 2013.

Foster, Daniel W. and J. Denis McGarry. "The Metabolic Derangements and Treatment of Diabetic Ketoacidosis." *Seminars in Medicine of the Beth Israel Hospital, Boston* 309.3 (1983): 159-169. Web. 25 Jan. 2013.

Gale, Edwin A.M. "The Rise of Childhood Type 1 Diabetes in the 20th Century." *Perspectives in Diabetes* 51 (2002): 3353-3361. Web. 29 Jan. 2013.

Juvenile Diabetes Research Foundation (JDRF). "Diabetes Complications." What is Diabetes? JDRF, 2013. Web. 25 Jan. 2013.

Juvenile Diabetes Research Foundation (JDRF). "Type 1 Diabetes Facts." Fact Sheets. JDRF, 2013. Web. 25 Jan. 2013.

Juvenile Diabetes Research Foundation (JDRF). "Leadership in Type 1 Diabetes Research." Research. JDRF, 2013. Web. 25 Jan. 2013.

Oxford English Dictionary. "Diabetes." Oxford: Oxford University Press, 2013. Web. 29 Jan. 2013.

Oxford English Dictionary. "Mellitus." Oxford: Oxford University Press, 2013. Web. 29 Jan. 2013.

National Diabetes Information Clearinghouse (NDIC). "Continuous Glucose Monitoring." U.S. Department of Health and Human Services. NIH, Dec. 2008. Web. 29 Jan. 2013.

Noble, Sara L., Elizabeth Johnston, and Bill Walton. "Insulin Lispro: A Fast-Acting Insulin Analog." *American Family Physician* 57.2 (1998): 279-286. Web. 29 Jan. 2013.

Pinkos, Arleen, Guillermo Arreaza-Rubin, William J. Heetderks, Ilan Irony, Hylton V. Joffe, Bruce Schneider, and Charles L. Zimliki. "FDA's proactive role in the development of an artificial pancreas for the treatment of diabetes mellitus." *Drug Discovery Today: Technologies* 4.1 (2007): 25-28. Web. 29 Jan. 2013.

Renard, Eric. "Insulin Delivery Route for the Artificial Pancreas: Subcutaneous, Intraperitoneal, or Intravenous? Pros and Cons." *Journal of Diabetes Science and Technology* 2.4 (2008): 735-738. Web. 29 Jan. 2013.

Renard, Eric, Guy Costalat, Hugues Chevassus, and Jacques Bringer. "Closed loop insulin delivery using implanted insulin pumps and sensors in type 1 diabetic patients." *Diabetes Research and Clinical Practice* 74 (2006): S173-S177. Web. 29 Jan. 2013.

Steil, G.M, A.E. Panteleon, K. Rebrin. "Closed-loop insulin delivery—the path to physiological glucose control." *Advanced Drug Delivery Reviews* 56 (2004): 125-144. Web. 29 Jan. 2013.

Steil, Garry M., et al. "Modeling β-Cell Insulin Secretion—Implications for Closed-Loop Glucose Homeostasis." *Diabetes Technology & Therapeutics* 5.6 (2003): 953-954. Web. 29 Jan. 2013.

University of California San Francisco (UCSF). "Blood Sugar and Stress." Diabetes Education Online. The Regents of the University of California, 2013. Web. 29 Jan. 2013.

U.S. Food and Drug Administration (FDA). "The Artificial Pancreas Device System (APDS)." Medical Devices. U.S. Department of Health and Human Services, 29 Jan. 2013. Web. 29 Jan. 2013.

Wilson, Val. "Diagnosis and treatment of diabetic ketoacidosis." *Emergency Nurse* 20.7 (2012): 14-18. Web. 29 Jan. 2013.