6 When Cells Are the Cure: Diabetes and Stem Cells

Disease is egalitarian: it strikes the privileged as well as the downtrodden, the youthful as well as the aged. Few children born in 1907 had the advantages in life of Elizabeth Evans Hughes. The daughter of Charles Evans Hughes, governor of New York, who later served as secretary of state and as a distinguished Chief Justice of the Supreme Court, Elizabeth was a bright and vivacious young girl. But by the summer of 1922 fourteen-year-old Elizabeth stood five feet tall yet weighed only forty-five pounds. She was so emaciated, her muscles so wasted, that she could barely walk. Elizabeth was dying of diabetes.

At the time of Elizabeth's diagnosis physicians had come to appreciate that diabetics could not properly metabolize their food and consequently were subject to weight loss, weakness, gangrene, infections, and other symptoms that often caused death within a year of diagnosis. Elizabeth's doctor, Frederick Allen, advocated a starvation diet for diabetes, which could hold off symptoms of the disease but resulted in a patient's wasting away. Diabetics faced a cruel choice: death by diabetes or death by starvation. Elizabeth's parents chose for her the latter, and the severe diet she was put on, at times supplying her with a meager three hundred calories a day, kept Elizabeth alive for three years after her symptoms became apparent.

Elizabeth had type 1 diabetes, also known as juvenile diabetes because it primarily strikes the young. Much more common is type 2 diabetes, also known as adult-onset diabetes because it appears in adulthood. Both types are characterized by the inability of cells to take up the sugar glucose from the blood following the digestion of food. Consequently, glucose accumulates to high levels in the blood, spills over into the urine, and is lost. The increased glucose load requires a larger-than-normal volume of

urine, leading to terrible thirst. Not getting enough nutrients, a diabetic becomes weak and tired, and is constantly hungry. Add to these problems the fact that glucose is actually a poison when it is present in the blood at higher-than-normal levels, and we can see why Elizabeth's disease was so devastating.

Glucose is a sugar that is the primary energy source for the cells of our body. Much as gasoline is burned by an automobile to produce the energy that propels it, glucose is "burned" to produce the energy that cells need to carry out their work. Some glucose we obtain directly—for example, from the sugar we put in our coffee or from the coating on our breakfast cereal—but most of it is obtained from the more complex food we eat as it is broken down by specialized cells in our gut.

The glucose that is released quickly finds its way to our bloodstream, where it flows to all cells in the body. Cells are prompted to take up glucose from the blood by the hormone insulin, a protein produced by the pancreas and released into the bloodstream after a meal to signal that glucose is now plentiful and needs to be disposed of.

Type 1 diabetes occurs when the immune system runs amok and attacks and kills the insulin-producing cells of the pancreas, so that little or no insulin is made, preventing other cells in the body from receiving the signal that glucose is available. Type 2 diabetes is due to an inability of cells to recognize the insulin signal, so they don't realize that they should take up the glucose that is in the bloodstream. As the glucose levels in the blood continue to rise, the pancreas must produce more insulin to keep up with the ever more urgent requirement to dispose of the extra glucose. The pancreas gets increasingly fatigued, and eventually gives up, leading to insulin-dependent diabetes, with its dire consequences.

By 1920, researchers knew that diabetes was due to a failure of pancreatic function: in diabetics, the pancreas still pumped digestive juices into the intestine, but it did not produce the secretion that went into the bloodstream to regulate metabolism. This secretion held the key to a possible therapy for diabetes, but its identity and nature were as yet unknown. At the University of Toronto, a young surgeon named Frederick Banting had a novel, albeit somewhat misguided, idea about how to obtain this internal secretion in an intact form, protected from the destructive effect of the pancreas's digestive juices.

Banting planned to test his idea on man's best friend. Beloved for their companionship, loyalty, and fun-loving nature, dogs have sometimes had to serve not as pets but as subjects of studies designed to cure serious diseases. Large enough for surgery, with a physiology that is a good match for that of humans, they are used when other animals such as mice won't do. Banting's plan was to tie off the ducts of the dogs' pancreases that empty the digestive juices into the gut, so as to prevent those juices from destroying what the pancreas secreted to manage blood glucose levels.

Banting believed that the cells making the digestive juices would wither away, while those that make the secretion that regulates glucose levels would be spared. He would then prepare an extract from these pancreases. At the same time, he would make other dogs diabetic by removing their pancreases, and then try to cure their disease by injecting them with the pancreas extract. Banting, together with his student, Charles Best, began injecting the diabetic dogs with pancreatic extracts, monitoring the dogs' blood glucose levels to determine whether the extract was effective.

It worked just as they had hoped: during a frenzied period of experimentation beginning in the summer of 1921, Banting and Best saw that the glucose levels in the blood of their diabetic dogs were lowered after they were injected with the pancreatic extracts. Extracts of cow pancreases (available in abundance from the nearby slaughterhouse) worked too. The success with the cows' pancreatic extracts indicated that the digestive ducts of the dogs' pancreases did not have to be tied off in complicated surgery. As Banting and Best later learned, there was never any danger that the destructive enzymes made by the pancreas would destroy the insulin in the secretion because they are produced in inactive, harmless forms that become active and destroy any proteins they encounter only after they are far from the pancreas.

But Banting never realized that his initial stroke of insight that ultimately led to the discovery of insulin was misguided. He went to his grave believing that a crucial contribution to the discovery of insulin was his idea to cripple the pancreas so that it couldn't secrete the digestive enzymes that (he thought) destroyed the prize he was after. As happens with many scientific breakthroughs, Banting got the right result for the wrong reason. Some scientists see their mistakes; others don't. Scientists can be as stubborn as anyone, and they often hold on to an idea long after others have

shown it to be far from reality. Yet even wrong ideas, if well implemented, can lead to great good.

Banting and Best were soon joined by the biochemist J. B. Collip, who worked out a procedure to purify the precious material, which they named "insulin." The name is based on the Latin root for the word "island," as the substance is derived from a special cluster of cells that form an island floating in the sea of the cells that make up the rest of the pancreas. At the end of 1921, Banting traveled to New Haven, Connecticut, to announce the exciting results of his experiments in a session for diabetes experts attending the annual meeting of the American Physiological Society. By May 1922, the Toronto group had engaged Eli Lilly and Company to produce insulin at the company's facilities in Indianapolis. Working with impressive speed, Lilly sent its first shipment of insulin to Toronto in July.

Banting examined the barely alive Elizabeth Hughes on August 16, 1922, and immediately started her on insulin. By the end of a week of treatment, she was put on a diet of 1,220 calories a day, and a week after that she was eating a normal diet of over 2000 calories. Even more remarkable to her, Elizabeth could again eat foods such as white bread, corn, and macaroni and cheese, all forbidden to her under her treatment by Dr. Allen. Descriptions of the first diabetics receiving insulin in the 1920s read much like those of AIDS patients in the first days of highly active retroviral drug treatment: a near miraculous recovery from the worst symptoms, a regain of weight back to their old levels, and a return to normal daily life.

Type 1 diabetes, accounting for 5 to 10 percent of diabetes cases, generally occurs in young people of normal weight. The antibodies that attack and destroy the insulin-producing cells of the pancreas may be triggered by a viral infection. Symptoms of the disease develop quickly, and treatment invariably requires regular injections of insulin.

The much more prevalent type 2 diabetes (about 90 percent of cases) has until recently mostly struck older people, the great majority of whom are overweight. The onset of the type 2 form is gradual, often requiring several years to become full-blown. Treatment includes weight loss, increased physical activity, blood glucose testing, and medication, either oral drugs or injected insulin.

The total incidence of diabetes is staggering: more than 7 percent of the American population has the disease! As we increasingly give in to the

drumbeat of the fast-food marketers to consume more high-fat, high-calorie foods, more and more of us, including our children, are learning that we have diabetes. We may like the convenience and low price of a quick meal, but what marketers avoid telling us is that eating too many burgers and fries and the like carries a heavy price. As affluent lifestyles, with their attendant high-fat, high-calorie diets, spread to countries such as India, whose traditional diet was lean, diabetes has become a worldwide epidemic.

As with most diseases, our personal DNA code plays a large role in our risk of contracting diabetes and in the course the disease takes if we get it. The genetics of diabetes is especially complex. The disease clearly runs in families: siblings of diabetics have a much higher risk of developing the disease than does the general population, and the identical twin of a diabetic—who shares her identical personal DNA code—is affected much more often than is a fraternal twin, who has a different personal DNA code.

The versions of genes that make up our DNA code influence other factors besides the initial risk of getting diabetes: how glucose is metabolized, what level of body mass is attained, and how the body responds to insulin are also highly heritable. It is not surprising, then, that some ethnic groups—who, as we'll discuss later, are more apt to share particular versions of their genes than are unrelated people—have relatively high rates of the disease: type 1 is especially frequent in people of European descent; type 2 is more prevalent in African Americans, Hispanic Americans, Native Americans, certain Asian Americans, and Pacific Islanders.

More than half of the genetic risk for type 1 diabetes is determined by a region of chromosome 6 that carries over one hundred genes. Many of these genes encode proteins that function in the immune system and might be responsible for its inappropriate attack on the insulin-producing cells that is the cause of the disease. These proteins sit on the outside surface of cells, acting as sentinels that continually examine proteins in the body and identify them as friend or foe. If the proteins are recognized as one's own, they are allowed to go on their way, but if they seem to come from an invader such as a virus or bacterium, they set off an alarm that triggers an immune response designed to eliminate the threat. Sometimes the alarm is so loud that other proteins—such as those in islet cells of the pancreas—are caught in the frantic response, and type 1 diabetes ensues.

In the case of type 2 diabetes, multiple genes contributing to the disease—or in many cases just regions of chromosomes where such genes may lie—have been identified, but their effects are usually small, and in some cases still uncertain. It seems likely that a large number of genes, influenced by such outside determinants as the type of diet and the amount of exercise a person gets, contribute to the onset of the disease and determine how it will progress. So far eleven genes have been conclusively identified as playing a role in type 2 diabetes, and more are sure to be forthcoming.

People with type 1 diabetes can be treated with insulin, but they can hardly be called cured. Diabetics must carefully monitor the level of glucose in their blood and inject themselves with insulin several times a day. But no matter how diligent they are in their surveillance, they must still closely control their diet and maintain their exercise regimen.

Even those who are able to maintain good control of their blood-glucose levels have difficulty keeping them constant; they experience episodes of extremely low blood sugar, which can result in loss of consciousness, and bouts of high blood sugar, which can eventually lead to blindness, cardiovascular disease, and other serious health problems. As a result of these complications, the life span of diabetics may be shortened by as much as one third.

Type 2 diabetes can often be controlled by diet and oral pharmaceuticals, but almost 20 percent of people with this form of the disease eventually require insulin therapy. Type 2 diabetics also develop an array of medical problems, most notably heart disease, depending on how well they are able to control their blood-sugar levels. Banting and Best's breakthrough saved the lives of Elizabeth Hughes and millions of others, but scientists are still searching for the new approaches that are desperately needed to treat and ultimately cure the disease.

Since the insulin-producing cells of the pancreas are destroyed in both types of diabetes, the disease might be cured if these cells could be replaced. Transplantation of pancreatic cells or of the entire pancreas from cadavers has been attempted, but there is a severe shortage of donors for this procedure.

Even if a donor can be found, a formidable roadblock is presented by the recipient's immune system, which recognizes the new cells as foreign and attacks them, and which therefore must be suppressed. But treatments for immune suppression often lead to other, quite unwelcome, complica-

tions. And even if the immune system can be fooled and the complications avoided, the refurbished pancreas provides insulin for only a limited amount of time, most recipients needing insulin injections again within a few years of receiving the transplant. Unfortunately, pancreatic cell transplantation is probably not a cure for this disease.

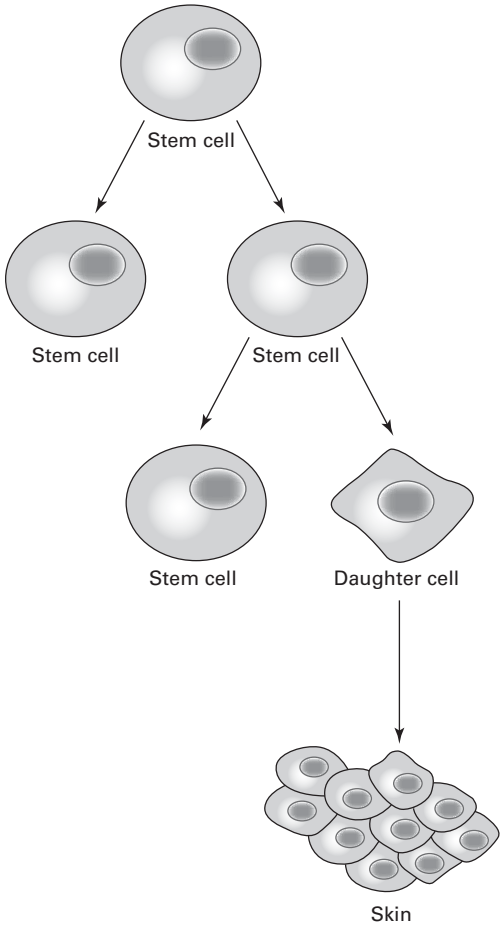
A wholly new avenue that shows promise is regenerative medicine: engineering a special type of cell—stem cells—to treat disease. Stem-cell therapy has been widely discussed in both scientific and public forums. If its promise is realized it could turn our aging bodies into a patchwork quilt of all kinds of different types of engineered cells. What are stem cells and how can we engineer them to provide material for organ or tissue replacement? What is the potential for this type of therapy in the treatment of human diseases?

As we saw in our discussion of human development in chapter 4, a fertilized egg goes on to produce a baby containing hundreds of different cell types by a continuing process of cell specialization. Once each cell becomes specialized—as a blood cell or a lung cell or a brain cell or a muscle cell—it is committed to that fate: there is no going back to the unspecialized, jack-of-all-trades state.

Stem cells, by contrast, have the extraordinary property of remaining unspecialized. But they can be coaxed to become any of several different specialized cell types. A stem cell can divide into two cells that remain as unspecialized stem cells over long periods of time, but under certain conditions a stem cell divides to produce a daughter cell that goes off into the world to make something of herself, embarking on a path toward specialization that eventually leads to life as a skin cell or a heart cell or any one of myriad other types of cell (see figure).

Stem cells exist in the embryo as well as the adult, but not all stem cells are created equal. Embryonic stem cells have the potential to give rise to every possible cell type and tissue: liver and lung, iris and intestine, skin and skeleton, and, of course, the pancreas and its insulin-producing cells.

As adults we also retain many kinds of stem cells in our bodies after our physical development is complete, but those are of limited potential. Adult stem cells have already started down the path of specialization, and as a consequence are restricted to becoming a narrow range of cell types. Adult stem cells in the bone marrow continuously produce new blood cells to



carry oxygen and fight infections; adult stem cells in the liver replenish the ones we damage on New Year's Eve; adult stem cells in the intestine and skin replace those that are continually sloughed off; adult stem cells in muscle provide replacements to the cells that are torn when we lift weights. We constantly lose cells for all kinds of reasons, and adult stem cells come to the rescue and provide replacements.

Even though certain adult stem cells can replenish certain organs throughout our lives, they cannot take up the slack when other types of cells are lost. Stem cells in the hair follicles of the skin give rise to hair and to epidermis, but not to brain cells; stem cells in the lining of the digestive tract give rise to several kinds of gut cells, but not to bone cells. The exis-

tence of stem cells for the pancreas is controversial, and even if they do exist it is uncertain whether they can be isolated and used to repopulate the pancreas.

Far more versatile are embryonic stem cells. These cells come from embryos only four or five days old—one source is left-over embryos from in vitro fertilization procedures that have been donated for research purposes. At that stage of development the embryo has only about one hundred to two hundred cells, and those cells have not yet begun their journey along the paths to specialization, so they are able to give rise to all of the cell types found in the adult. These stem cells could potentially be an unlimited source of insulin-producing cells.

But they are not available yet. A number of hurdles must be cleared before embryonic stem cells can be used to cure diabetes. First, new embryonic stem-cell lines must be obtained, because almost all the existing ones are flawed. Many seem to have limited potential, being able to give rise to only certain types of cells. Worse, many of the stem-cell lines that exist today are contaminated, precluding their use in humans. They were grown on a layer of mouse cells, to provide factors necessary for stem cell growth. Those growth factors have now been identified and can be provided in pure form. Biologists have learned much about the care and handling of embryonic stem cells in the last several years, promising healthier, more versatile, and more consistent stem-cell lines in the future.

Second, embryonic stem cells need to be coaxed into specializing as insulin-producing pancreatic cells, and the persuasion has to be gentle, done in a way that mimics the process that takes place in the developing embryo. As embryonic cells specialize to become pancreatic islet cells, different genes are expressed in a carefully choreographed process directed by a few key proteins—the transcription factors we learned about in chapter 4—that recognize and bind to sequences of DNA in the genes necessary to produce pancreatic cells and control the expression of those genes. Activation of such genes eventually leads to production of the proteins that turn a cell into one that produces insulin.

Third, once conditions are established for coaxing stem cells to specialize in insulin production, the process needs to be made easy and reliable. Huge numbers of cells will be required for therapy, so growing them in small plastic dishes as is done today will not be up to the task; cells will need to be grown in large vats to meet the need. Furthermore, the

treatments to direct cell specialization must become highly efficient, because cells that resist the nudge and remain unspecialized have the potential to grow into tumors when implanted into a recipient.

Finally, the problem of rejection by the recipient's immune system must be overcome, so that individuals being treated do not destroy the insulin-secreting cells they receive. A possible solution is to establish banks of embryonic stem-cell lines from different people. A doctor treating a diabetic would withdraw from the bank a cell line that is compatible with the recipient. An alternative would be to genetically engineer changes in the cell surface proteins (the ones monitored by the immune system) of embryonic stem cells so they are not recognized as foreigners by the patient's immune system.

In addition to the daunting scientific issues, challenging ethical issues surround human embryonic stem-cell research. Fertilized human eggs must be destroyed to produce new stem-cell lines. For those who believe that a fertilized egg has the same standing as a human being, its destruction poses a moral dilemma. For those who believe that an embryo has the full rights of a living human, the use of embryos in research may not be acceptable.

Many others—and we count ourselves among them—believe that scientists have a duty to prevent or alleviate human suffering, with the utmost importance placed on saving the lives of people already among us. An embryo consisting of one hundred to two hundred cells—about the size of the period at the end of this sentence—has no brain or central nervous system and no other organs associated with a person. This lack of sentience is an argument that this tiny embryo should not have the same status and rights as a living person. Of course, the embryo must be given serious respect, and strict controls must be in place to limit its use to research that can benefit humanity. But we should not abandon the tremendous potential of embryonic stem cells for curing disease.

We think reasonable people should be able to agree on guidelines and regulations to govern the use of human embryos. We do not see why the more than 400,000 embryos that currently rest in freezers and are destined to be destroyed or remain frozen indefinitely cannot be donated for research that has the potential to alleviate human suffering.

In our view, embryonic stem cells have tremendous promise, and scientists should be encouraged to pursue this important line of research. In

addition to diabetes, a host of other devastating diseases and disabilities—Alzheimer's disease, Parkinson's disease, heart disease, arthritis, spinal cord injuries, burns, and vision and hearing loss, to name just a few—are potentially treatable by regenerative medicine.

A promising alternative to embryonic stem cells has recently burst onto the scene. Scientists have discovered that turning on just a few genes in adult cells that are committed to a specialized function can "reprogram" them to return to an earlier, unspecialized stem-cell-like state. These genes encode transcription factors that act as master switches able to change the fate of cells. The reprogrammed cells, known as induced pluripotent stem cells, or iPS cells, behave much like embryonic stem cells. Because iPS cells are derived from adult cells and thus can be obtained without the destruction of fertilized eggs, they may provide a noncontroversial approach to regenerative medicine. But the arguments about the use of embryonic stem cells are not going to abate soon: if biologists are to learn how closely iPS cells mimic embryonic stem cells, they must be able to produce and study both types of cells. For now, at least, stem cells derived from human embryos should not be abandoned in our quest for cures.

In 1930, after Elizabeth Evans Hughes's miraculous recovery from near death after treatment with some of the first doses of insulin, she married William T. Gossett, a lawyer for Ford Motor Company, and they had three children. In 1980, when the writer Michael Bliss wrote to her husband to ask how Elizabeth had died, he received a response from Elizabeth Hughes Gossett herself. She was in fine health, physically and intellectually, and she met with Bliss to reminisce about her nightmarish youth with diabetes. She died in 1981 at the age of seventy-three, having survived the disease for sixty years, and after taking more than forty thousand injections of insulin.

We look forward to the time when a young person newly diagnosed with diabetes will receive just one injection: of insulin-producing cells derived from embryonic stem cells or iPS cells, and thereafter will enjoy a healthy life without ever having to poke herself with a needle.

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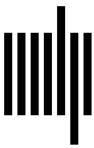

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