Insulin Dependent Diabetes Mellitus (Type 1 Diabetes)

Our eighteen (18) year old son (the youngest of three [3] boys) had just graduated in June, 2009 from high school and was taking an Introductory Accounting class at San Jose City College in preparation for his matriculation at the University of Arizona in the fall. In his final year in high school he had showed periodic symptoms of irritability, fatigue, hunger, weight loss and lethargy. This all seemed to come to a head on July 11, 2009 when he was feeling particularly tired. One morning he complained of extreme thirst and dry mouth. Having some knowledge of these symptoms, we decided to test his blood sugar with a glucose meter we had in the house. The reading came back as "out of range" on the upper limit (over 660 mg/dL). We checked and double checked this reading with newer test strips, but the readings came back the same. Our next step was to take our son into the urgent care clinic. At the clinic, his glucose reading was 828 mg/dL, more than eight times the normal reading.

Our son was diagnosed with insulin dependent diabetes mellitus (IDDM) Type 1 and immediately admitted to intensive care at El Camino Hospital. He spent four days in the hospital as the doctor's worked to get his glucose back to normal levels. After he was discharged, we spent the next several weeks in a crash course on learning how to manage IDDM before our son headed off to college. Needless to say, this whole incident raised many questions in my mind as to why this happened. Neither my wife nor I had a history of IDDM in our families that we knew of. One of my motivations in taking *Your Genes and Your Health* was to try and find out more information about the genetic nature of this disease and learn about the current and future genetic risk in our family for this disease.

Classic Diagnosis and Treatment

The human body requires insulin to move blood sugar (glucose) into cells. Blood sugar provides a source of energy for cells. Without blood sugar, cells are unable to perform their normal function to create energy for the body. The pancreas produces the main hormones, insulin and glucagon, needed for this process. "These hormones help to regulate the amount of sugar found in the blood and the body's cells. The body's cells need energy to function. The most readily available form of energy is glucose, a type of sugar. Insulin helps to take glucose from the blood into the cells themselves. This allows the cells to function properly. Glucagon stimulates cells in the liver to release glucose into the blood when levels are low" [The Pancreas, 1]. IDDM is a chronic illness with no known cure. Type 1 diabetes occurs most often in children and young adults. Insulin that is normally produced by beta cells in the pancreas is destroyed by an autoimmune process. There is evidence that this disease has a genetic component to it and thus can be passed from one generation to the next.

"Diabetes is diagnosed with the following blood tests:

- Fasting blood glucose level -- diabetes is diagnosed if it is higher than 126 mg/dL two times
- Random (nonfasting) blood glucose level -- you may have diabetes if it is higher than 200 mg/dL, and you have symptoms such as increased thirst, urination, and fatigue (this must be confirmed with a fasting test)

- Oral glucose tolerance test -- diabetes is diagnosed if the glucose level is higher than 200 mg/dL after 2 hours

- Hemoglobin A1c test
  - Normal: Less than 5.7%
  - Pre-diabetes: Between 5.7% and 6.4%
  - Diabetes: 6.5% or higher" [MedlinePlus, 2].

Type 1 diabetics must take daily injections to provide the insulin needed for proper cell functioning. There are a number of insulin types, including fast acting insulin (Novalog®) and slowing acting insulin (Levemir®). The amount of insulin a patient needs to take each day depends on the amount of food consumption (carbohydrates) and physical exercise they undertake. Diabetics must learn how to stabilize their food consumption and exercise routines to help better determine the quantity and frequency of injections. Diabetics must also guard against low blood sugar known as hypoglycemia (< 70 mg/dL). In such cases a diabetic needs to consume sugars to get their blood sugar level up.

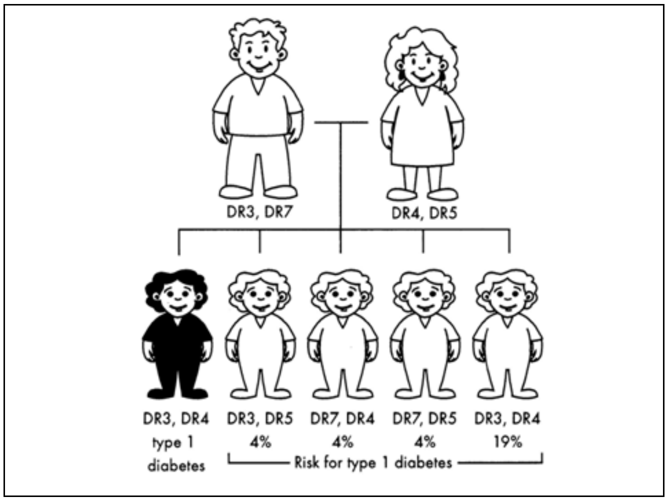
Failure to maintain proper blood sugar levels can lead to serious complications for Type 1 diabetics, including the following:

- Coronary artery disease and stroke
- Nephropathy (kidney damage)
- Neuropathy (nerve damage)
- Foot ulcers and amputations
- Retinopathy (eye complications)
- Osteoporosis
- Infections.

Genetics of IDDM Type 1

The genetics of Type 1 diabetes is complicated and not all gene mutations that might put a person at risk for Type 1 diabetes have been catalogued or understood. Researchers have not yet identified all the gene mutations that put a person at risk for Type 1 diabetes. There are twenty (20) different genes that can affect a person's risk for Type 1 diabetes [Adams, 3]. Chromosome 6 in the HLA structure has over 200 genes that play a role in determining susceptibility to Type 1 diabetes.

Two (2) specific genes seem to have a higher level of involvement in Type 1 diabetes. The first is the human leukocyte antigen (HLA) region and the second is the insulin gene. "The HLA (human leukocyte antigen) region is a section of a chromosome that contains several genes that are involved in how the immune system works. These genes make proteins that dot the surface of some cells in the immune system. These proteins are important in order for the immune system to distinguish between its own cells and an infectious agent, such as a bacteria or virus. When this system fails, the immune cells attack other cells of the body (such as pancreas cells) in a process called an autoimmune reaction" [Adams, 4]. One gene in this region that seems to be influential in Type 1 diabetics is referred to as DR, specifically DR3 and DR4. Ninety-five percent (95.0%) of Type 1 diabetics have inherited DR3 and DR4 [Adams, 4]. The chart below summarizes the risk profile for Type 1 diabetes depending on the HLA genetic profiles of one's parents:



Source: S. Serjeantson (1994). The Genetics of Diabetes.

The following table summarizes the predisposition to Type 1 diabetes:

Family Situation	Risk for Developing Type 1 Diabetes
In the general population	1 in 300
When a brother or sister is affected and they do not have the same HLA combination	1 in 100
When a parent is affected	1 in 25
When a brother or sister is affected	1 in 14
When a brother or sister is affected and they have the same combinations for 2 or more of the HLA genes	1 in 6
When a brother or sister and a parent or child is affected	1 in 6
When an identical twin is affected	1 in 3

Source: Center for Genetics Education. Diabetes Type 1 and 2 and Inherited Predisposition

Despite one's HLA genetic predisposition, other factors can trigger Type 1 diabetes, including "viruses, interactions with the information in other genes or other unknown environmental factors" [Centre for Genetics Information, 3]. One possible theory is that "an unidentified virus stimulates an autoimmune attack against the cells of the pancreas that produce insulin in some genetically predisposed people" [Centre for Genetics Information, 3]. Some viruses that have been linked to Type 1 diabetes include Epstein-Barr, coxsackievirus, mumps and cytomegalovirus. Each of these might trigger autoimmune destruction of islet cells [Mayo Clinic Staff, 3].

Another possible explanation for Type 1 diabetes is the insulin gene. "The insulin gene is the region of DNA that codes for the protein insulin. Changes in DNA near the insulin gene seem to influence a person's susceptibility to diabetes. This region, which is different lengths in different people, determines how much insulin the gene makes. It is composed of a repeated section of DNA called the Variable Number of Tandem Repeats (VNTR). Smaller VNTR regions contain only 26 to 63 DNA repeats, while long regions contain 140 to 200 repeats. If a person inherits two short VNTR regions, they are two to five times more likely to develop Type 1 diabetes than a person with at least one long VNTR" [Adams, 4].

<u>Novel Diagnoses or Treatments Resulting from the Genetic Information</u>

Type 1 diabetics are required to constantly monitor their blood sugar levels and insulin injections are required to bring it within therapeutic ranges. Blood sugar should be maintained during the day between 80 mg/dL and 120 mg/dL before food is consumed and one (1) to two (2) hours after consumption. At bedtime blood sugar should be maintained between 100 mg/dL and 140 mg/dL [The Mayo Clinic, 6]. When outside these ranges, insulin therapy is called for. This requires injections of insulin which is available in the market today in several different forms, including fast-acting, long-acting and intermediate acting.

For several years now insulin pumps have been available on the market. These devices, which are about the size of a cell phone, deliver fast-acting insulin 24 hours per day through a catheter inserted under the abdominal skin. Insulin doses are separated into:

- Basal rates (continuous delivery over 24 hours to keep blood sugar within range between meals and during sleep).
- Bolus doses required to counteract sugar produced by carbohydrates consumed in meals.
- Other doses to bring blood sugar back in range [Living With Diabetes, 1].

Type 1 diabetics have to also be on guard for hypoglycemia, which occurs when blood sugar levels drop below the target ranges. Hypoglycemia is a serious condition that can lead to unconsciousness. Consuming fast-acting sugar can potentially remedy this condition. Another option is to perform an emergency injection of glucagon, a "hormone that stimulates the release of sugar in the blood" [Mayo Clinic Staff, 12].

Some novel treatments / cures for Type 1 diabetes are currently in clinical trials several of which are summarized below:

<u>Pancreas Transplant</u>

This involves replacing one's pancreas with a donor pancreas. "Each year, approximately 1,300 people with type 1 diabetes receive whole-organ pancreas transplants. After a year, 83 percent of these patients, on average, have no symptoms of diabetes and do not have to take insulin to maintain normal glucose concentrations in the blood" [Stem Cells and Diabetes, 1]. There are a number of potential negative side effects to a pancreas transplant, the most serious of which is rejection. This procedure requires the patient to adhere to a life-long therapy of immune suppression drugs which have a number of harmful side effects.

<u>Islet Cell Transplants</u>

This procedure involves the transplanting islet cells from a donor pancreas. Similar to a pancreas transplant, immune suppression drug therapy is required. "However, the requirement for steroid immunosuppressant therapy to prevent rejection of the cells increases the metabolic demand on insulin-producing cells and eventually they may exhaust their capacity to produce insulin. The deleterious effect of steroids is greater for islet cell transplants than for whole-organ transplants. As a result, less than 8 percent of islet cell transplants performed before last year had been successful" (Stem Cells and Diabetes, 1].

Gene Therapy

There are some very interesting clinical trials that show promise in the area of stem cell transplants. A team from Baylor College has recently had success in using gene therapy to stimulate the formation of new beta cells in the liver using neurogenin3. In addition, they added an islet growth factor gene called betacellulin to stimulate grow of new islets [Gene Therapy Reverses Type 1 Diabetes in Mice, Study Finds, 1].

In another study from Children's Hospital of Pittsburg and Pittsburgh Medical Center, it was "shown that type 1 diabetes can be reversed in a mouse model. The scientists extracted the mouse's dendritic cells from the blood and enhanced them with specific molecule blockers. They then reinjected them into the mouse. This procedure stopped the process that kills beta cells, by blocking the T cells which attack them. A series of injections over the course of several weeks interrupted the T cell attack on the beta cells of the pancreas and allowed the beta cells to regenerate. This resulted in the pancreas of the mice producing insulin again" [Manzella, 1].

Another research team at the Universität Autònoma de Barcelona (UAB) has cured Type 1 diabetes in dogs. The dogs were given injections that introduced "gene therapy vectors, with a dual objective: to express the insulin gene, on the one hand, and that of glucokinase, on the other. Glucokinase is an enzyme that regulates the uptake of glucose from the blood. When both genes act simultaneously they function as a "glucose sensor", which automatically regulates the uptake of glucose from the blood, thus reducing diabetic hyperglycemia (the excess of blood sugar associated with the disease)" [UAB Researchers Cure Type 1 Diabetes in Dogs, 1].

Gene therapy seems to offer particular promise in developing potential cures for Type 1 diabetes.

Final Thoughts

My wife and I have both recently registered with *23andMe* to see if we can learn more about our respective genetic backgrounds and any impact this may have had on our son's predisposition to Type 1 diabetes. We are still awaiting the results. This is a difficult disease, but fortunately it is very manageable. The clinical trials and research into the causes and cures for Type 1 diabetes show promise and we are hopeful that our son can someday be cured of this disease and lead a life free of insulin therapy.

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