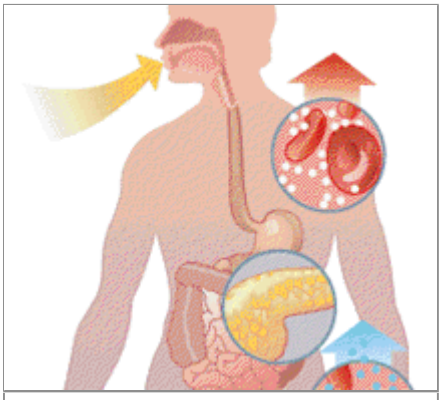
# Diabetes Mellitus

## INTRODUCTION

Diabetes Mellitus, disease in which the pancreas produces little or no insulin, a hormone that helps the body's tissues absorb glucose (sugar) so it can be used as a source of energy. The condition may also develop if muscle, fat, and liver cells respond poorly to insulin. In people with diabetes, glucose levels build up in the blood and urine, causing excessive urination, thirst, hunger, and problems with fat and protein metabolism. Diabetes mellitus differs from the less common diabetes insipidus, which is caused by lack of the hormone vasopressin that controls the amount of urine secreted.





**How Diabetes Mellitus Develops**

The hormone insulin, made in the pancreas, helps control levels of the sugar glucose, which is needed to fuel many chemical processes. In a healthy person, when food is digested *(1)*, glucose levels in the bloodstream rise *(2)*. The pancreas releases insulin *(3)*, which helps body cells take up glucose. Insulin also helps convert glucose into glycogen, which is stored in the liver *(4)* and muscles until needed for fuel. Hormones regulate the release of insulin by causing blood sugar levels to drop *(5)*, which in turn causes the pancreas to secrete less insulin *(6)*. In a person with diabetes mellitus, the pancreas produces insufficient levels of insulin or the body is unable to use the insulin it makes. After food is digested *(A)*, if the pancreas cannot produce enough insulin *(B)*, the body is forced to break down fats instead of glucose for energy. Poisonous chemicals called ketones are excreted in the urine *(D)* and also build up in the bloodstream *(E)*, leading to ketoacidosis, a serious condition that may cause coma or death. If the body is unable to use insulin properly, glucose is locked out of cells and circulates through the body without being absorbed. High levels of sugar in the blood *(C)* and urine *(D)* impair the body's ability to fight infections and may lead to ketoacidosis.

In the United States, about 16 million people (6 percent of the population) suffer from diabetes mellitus. Every year, about 800,000 people learn they have the disease. Diabetes mellitus kills about 193,000 U.S. residents each year, and it is the seventh leading cause of all deaths and the sixth leading cause of all deaths caused by disease. In Canada, more than 2.2 million residents (7 percent of the population) have diabetes mellitus, and the disease contributes to more than 25,000 deaths a year.

Diabetes is most common in adults over 45 years of age; in people who are overweight or physically inactive; in individuals who have an immediate family member with diabetes; and in people of African, Hispanic, and Native American descent. The highest rate of diabetes in the world occurs in Native Americans. More women than men have been diagnosed with the disease.

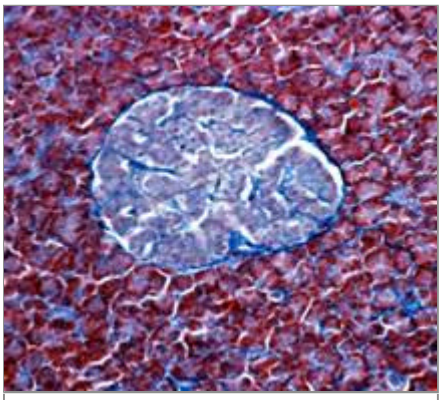


Photo Researchers, Inc./Astrid and Hanns-Frieder Michler

**Insulin Secretion**

This light micrograph of a section of the human pancreas shows one of the islets of Langerhans, *center,* a group of modified glandular cells. These cells secrete insulin, a hormone that helps the body metabolize sugars, fats, and starches. The blue and white lines in the islets of Langerhans are blood vessels that carry the insulin to the rest of the body. Insulin deficiency causes diabetes mellitus, a disease that affects at least 10 million people in the United States.

In diabetes mellitus low insulin levels prevent cells from absorbing glucose. As a result, glucose builds up in the blood. When glucose-laden blood passes through the kidneys, the organs that remove blood impurities, the kidneys cannot absorb all of the excess glucose. This excess glucose spills into the urine, accompanied by water and electrolytes—ions required by cells to regulate the electric charge and flow of water molecules across the cell membrane. This causes frequent urination to get rid of the additional water drawn into the urine; excessive thirst to trigger replacement of lost water; and hunger to replace the glucose lost in urination. Additional symptoms may include blurred vision, dramatic weight loss, irritability, weakness and fatigue, and nausea and vomiting.

## TYPE 1 DIABETES

Diabetes is classified into two types. In Type 1 diabetes, formerly called insulin-dependent diabetes mellitus (IDDM) and juvenile-onset diabetes, the body does not produce insulin or produces it only in very small quantities. Symptoms usually appear suddenly, typically in individuals under 20 years of age. Most cases occur around puberty—around age 10 to 12 in girls and age 12 to 14 in boys. In the United States Type 1 diabetes accounts for 5 to 10 percent of all diabetes cases. In Canada, Type 1 diabetes accounts for about 10 percent of all diabetes cases.

Type 1 diabetes is considered an autoimmune disease because the *immune system* (system of organs, tissues, and cells that rid the body of disease-causing organisms or substances) attacks and destroys insulin-producing cells, known as beta cells, in the pancreas. Scientists believe that a combination of

genetic and environmental factors may somehow trigger the immune system to destroy these cells. Scientists have so far identified 20 genes that play a role in Type 1 diabetes, although the exact function of these genes is still under investigation. Environmental factors, such as certain viruses, may also contribute to the development of the disease, particularly in people who already have a genetic predisposition for the disease.

Untreated Type 1 diabetes affects the metabolism of fat. Because the body cannot convert glucose into energy, it begins to break down stored fat for fuel. This produces increasing amounts of acidic compounds in the blood called ketone bodies, which interfere with cellular respiration, the energy-producing process in cells.

## III TYPE 2 DIABETES

In Type 2 diabetes, formerly known as non-insulin-dependent diabetes mellitus (NIDDM) and adult-onset diabetes, the body's delicate balance between insulin production and the ability of cells to use insulin goes awry. Symptoms characteristic of Type 2 diabetes include those found in Type 1 diabetes, as well as repeated infections or skin sores that heal slowly or not at all, generalized tiredness, and tingling or numbness in the hands or feet.

Of the nearly 16 million people in the United States with diabetes, 90 to 95 percent (about 15 million people) have Type 2 diabetes. About 90 percent of all diabetes cases in Canada are Type 2. The onset of Type 2 diabetes usually occurs after the age of 45, although the incidence of the disease in younger people is growing rapidly. Because symptoms develop slowly, individuals with the disease may not immediately recognize that they are sick. A number of genes work together to cause Type 2 diabetes. In addition, scientists believe that there is a strong relationship between obesity and Type 2 diabetes. About 80 percent of diabetics with this form of the disease are significantly overweight.

## IV COMPLICATIONS

National Eye Institute

**Vision Loss from Diabetic Retinopathy**

People with diabetes mellitus are at risk of developing the vision disorder known as diabetic retinopathy. This condition occurs as a result of damage to the small blood vessels in the retina—the light-sensitive lining at the back of the eye. Symptoms may include blurred central or side vision, or a blind spot in the central vision. Prompt medical treatment can prevent this condition from worsening.

If left untreated, diabetes mellitus may cause life-threatening complications. Type 1 diabetes can result in diabetic coma (a state of unconsciousness caused by extremely high levels of glucose in the blood) or death. In both Type 1 and Type 2 diabetes, complications may include blindness, kidney failure, and heart disease. Diabetes can cause tiny blood vessels to become blocked; when this occurs in blood vessels of the eye, it can result in *retinopathy* (the breakdown of the lining at the back of the eye), causing blindness. Diabetes mellitus is the leading cause of new cases of blindness in people aged 20 to 74. When diabetes affects the kidney it is called *nephropathy* (the inability of the kidney to properly filter body toxins). About 40 percent of new cases of end-stage *renal disease* (kidney failure) are caused by diabetes mellitus. Blockages of large blood vessels in diabetics can lead to many cardiovascular problems, including high blood pressure, heart attack, and stroke. Although these conditions also occur in nondiabetic individuals, people with diabetes are two to four times more likely to develop cardiovascular disorders.

Diabetes mellitus may also cause loss of feeling, particularly in the lower legs. This numbness may prevent a person from feeling the pain or irritation of a break in the skin or of foot infection until after complications have developed, possibly necessitating amputation of the foot or leg. Burning pain, sensitivity to touch, and coldness of the foot, conditions collectively known as neuropathy, can also occur. Other complications include higher-risk pregnancies in diabetic women and a greater occurrence of dental disease.

## V DIAGNOSIS AND TREATMENT

Diabetes is detected by measuring the amount of glucose in the blood after an individual has fasted (abstained from food) for about eight hours. In some cases, physicians diagnose diabetes by administering an oral glucose tolerance test, which measures glucose levels before and after a specific amount of sugar has been ingested. Another test being developed for Type 1 diabetes looks for specific *antibodies* (proteins of the immune system that attack foreign substances) present only in persons with diabetes. This test may detect Type 1 diabetes at an early stage, reducing the risk of complications from the disease.

Once diabetes is diagnosed, treatment consists of controlling the amount of glucose in the blood and preventing complications. Depending on the type of diabetes, this can be accomplished through regular physical exercise, a carefully controlled diet, and medication.

Individuals with Type 1 diabetes require insulin injections, often two to four times a day, to provide the body with the insulin it does not produce. The amount of insulin needed varies from person to person and may be influenced by factors such as a person's level of physical activity, diet, and the

presence of other health disorders. Typically, individuals with Type 1 diabetes use a meter several times a day to measure the level of glucose in a drop of their blood obtained by pricking a fingertip. They can then adjust the amount of insulin injected, physical exercise, or food intake to maintain the blood sugar at a normal level. People with Type 1 diabetes must carefully control their diets by distributing meals and snacks throughout the day so as not to overwhelm the ability of the insulin supply to help cells absorb glucose. They also need to eat foods that contain complex sugars, which break down slowly and cause a slower rise in blood sugar levels.

Although most persons with Type 1 diabetes strive to lower the amount of glucose in their blood, levels that are too low can also cause health problems. For example, if a person with Type 1 diabetes injects too much insulin, it can produce low blood sugar levels. This may result in hypoglycemia, a condition characterized by shakiness, confusion, and anxiety. A person who develops hypoglycemia can combat symptoms by consuming food that contains sugar, such as glucose tablets, fruit juice, or hard candy.

In order to control insulin levels, people with Type 1 diabetes must monitor their glucose levels several times a day. In 1983 a group of 1,441 Type 1 diabetics aged 13 to 39 began participating in the Diabetes Control and Complications Trial (DCCT), the largest scientific study of diabetes treatment ever undertaken. The DCCT studied the potential for reducing diabetes-related complications, such as nerve or kidney disease or eye disorders, by having patients closely monitor their blood sugar levels four to six times a day, maintaining the levels as close to normal as possible. The results of the study, reported in 1993, showed a 50 to 75 percent reduction of diabetic complications in people who aggressively monitored and controlled their glucose levels. Although the study was performed on people with Type 1 diabetes, researchers believe that close monitoring of blood sugar levels would also benefit people with Type 2 diabetes.

For persons with Type 2 diabetes, treatment begins with diet control, exercise, and weight reduction, although over time this treatment may not be adequate. People with Type 2 diabetes typically work with nutritionists to formulate a diet plan that regulates blood sugar levels so that they do not rise too swiftly after a meal. A recommended meal is usually low in fat (30 percent or less of total calories), provides moderate protein (10 to 20 percent of total calories), and contains a variety of carbohydrates, such as beans, vegetables, and grains. Regular exercise helps body cells absorb glucose—even ten minutes of exercise a day can be effective. Diet control and exercise may also play a role in weight reduction, which appears to partially reverse the body's inability to use insulin.

For some people with Type 2 diabetes, diet, exercise, and weight reduction alone may work initially, but eventually this regimen does not help control high blood sugar levels. In these cases, oral medication may be prescribed. If oral medications are ineffective, a person with Type 2 diabetes may need insulin injections or a combination of oral medication and insulin injections. About 49 percent of individuals with Type 2 diabetes require oral medications, 40 percent require insulin injections or a combination of insulin injections and oral medications, and 10 percent use diet and exercise alone.

## VI CURRENT RESEARCH

At present no cure exists for diabetes, and scientists are unsure of the exact cause, although

researchers are investigating a combination of genetic and environmental factors. So far researchers have identified 20 genes involved in Type 1 diabetes, and they are working to determine each gene's role in causing the disease. The inheritance patterns of Type 1 diabetes are complicated, with many different genes influencing a person's risk. For instance, a gene known as DR plays a role in Type 1 diabetes. Two forms of this gene, called DR3 and DR4, are present in 95 percent of people with Type 1 diabetes. People who inherit DR3 alone develop diabetes at an older age and have antibodies that destroy insulin-producing beta cells. Those who inherit DR4 tend to develop diabetes earlier in life and have antibodies that destroy insulin. A person with both DR3 and DR4 typically develops diabetes at a very young age and has the highest level of insulin-destroying antibodies.

In 2000 researchers were surprised to find that a variation of a gene called Caplain-10, which is not involved in glucose metabolism, is associated with the development of Type 2 diabetes. One form of this gene produces a small amount of protein, and researchers are studying how this decrease in protein increases a person's risk for diabetes. Other genetic studies indicate that certain genes cause a variation of Type 2 diabetes called maturity onset diabetes of the young (MODY), which develops in people under the age of 25. Although scientists do not yet understand how these genes cause MODY, the genes are known to be active in the liver, intestine, kidney, and pancreas.

Other scientists hope to identify the environmental factors that trigger Type 1 diabetes in people with a genetic predisposition for the disease. If they can determine what causes the immune system to attack the cells that produce insulin, they may discover how to prevent the condition from developing. For instance, studies suggest that certain viruses, such as coxsackie B, rubella, and mumps, may trigger an immune reaction against beta cells or in some cases directly infect and destroy these cells.

Researchers attribute most cases of Type 2 diabetes to obesity. Studies show that the risk for developing Type 2 diabetes increases by 4 percent for every pound of excess weight a person carries. Researchers are investigating the exact role that extra weight plays in preventing the proper utilization of insulin and why some overweight people develop the disease while others do not.

Research also focuses on transplanting a healthy pancreas or its insulin-producing beta cells into a person with Type 1 diabetes to provide a natural source of insulin. Some patients who have received pancreas transplants have experienced considerable improvements in their health, but positive, long-term results with beta-cell transplants have not yet occurred. In both types of transplants recipients must take drugs that suppress their immune systems so the body will not reject the new pancreas or cells. These drugs can cause life-threatening side effects because the patient's body can no longer protect itself from other harmful substances. In most people with diabetes, these drugs pose a greater risk to health than living with diabetes. Scientists are also studying the development of an artificial pancreas and ways to genetically manipulate non-insulin-producing cells into making insulin.

New methods for accurately measuring blood glucose levels may improve the quality of life for many individuals with diabetes. New techniques include the use of laser beams and infrared technology. For example, a tiny computer using infrared light can be used to measure a person's blood sugar level. The computer automatically delivers the reading to an insulin pump carried on the diabetic's body that injects the appropriate amount of insulin.

Other advances include new drugs that control blood sugar. In April 2000 the United States Food and Drug Administration (FDA) approved glargine, an insulin drug that needs to be injected only once a day. Sold under the brand name Lantus, this drug can be used by people with Type 1 diabetes, as well as by those with Type 2 diabetes who require insulin injections. A number of drugs have been developed to help people with Type 2 diabetes. Examples include acarbose, (sold under the brand name Precose), which controls blood sugar by slowing the digestion of carbohydrates, and metformin (sold under the brand name Glucophage), which controls liver production of sugar, causes weight loss, and reduces total cholesterol. In 2000 the FDA removed the drug troglitazone (sold under the brand name Rezulin) from the market. Although the drug enhances the ability of cells to use glucose, it was found to produce severe liver toxicity.