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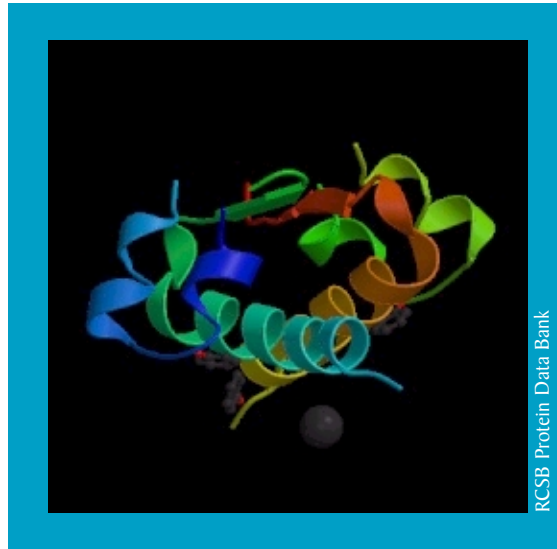
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DIABETES



Structure of human insulin hexamer.

- **Diabetes afflicts an estimated 18 million Americans and over 135 million people worldwide.**
- **Diabetes is the 6th leading cause of death by disease in the United States.**
- **Each year nearly 800,000 people are diagnosed with diabetes, and nearly 200,000 people die from the disease annually.**
- **Diabetes and its complications occur among Americans of all ages and racial/ethnic groups. About 18 percent of Americans 65 years of age and older have diabetes.**
- **Diabetes patients risk debilitating complications, such as blindness, kidney disease, heart disease and stroke. Diabetes is the leading cause of blindness among adults between the ages of 20 and 74 years of age.**
- **Annual costs related to diabetes, both direct medical costs and indirect costs (disability, work loss), are estimated at more than \$132 billion.**
- **Diabetes also affects animals and has been diagnosed in virtually every breed of dog and cat in the U.S.**

Diabetes mellitus (or simply, diabetes) is a disease caused by the body's failure to produce or effectively use the crucial hormone **insulin**. **Hormones** are substances that help control the activities of cells.

Normally during digestion, the body changes sugars and other nutrients into a form of sugar called **glucose**. The blood carries glucose to cells in the body and insulin helps change it into energy for cells to use. This process of changing food into energy is what all living things depend on to survive. When a person or animal has diabetes, something goes wrong in the process of turning food into energy.



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Words contained in the glossary (pages 11-12) are highlighted in **bold** the first time they appear in the text.

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DIABETES, page 2

There are two types of diabetes. In type 1, or early-onset diabetes, the **islets of Langerhans** in the **pancreas** are destroyed and the body cannot make insulin. Patients with type 1 diabetes require insulin injections to control their blood sugar. In type 2, sometimes known as adult-onset diabetes, the body makes some insulin but either makes too little or has difficulty using it, a phenomenon known as **insulin resistance**.

When insulin cannot perform properly, the glucose in the blood cannot be used by cells to make energy and it collects in the blood. This leads to high blood sugar levels and can cause serious health problems. In children, if not treated, diabetes can be fatal within a short time. In older patients, diabetes may go undetected for long periods. Complications such as blindness, kidney failure, loss of limbs, heart disease, and stroke can occur in patients both young and old.

Although there is no cure yet for diabetes, with early diagnosis, proper treatment and good patient control over blood sugar levels, the health complications related to diabetes can be minimized.

Almost all human diseases exist in at least one other species, and diabetes is no exception. Roughly one in every 500 dogs or cats has diabetes. Guinea pigs and rabbits also develop diabetes naturally, as do nonhuman primates. In companion animals with diabetes, progression of the disease can sometimes be controlled through proper diet and exercise. However, as with people, many others require insulin injections to keep their diabetes in check.



How have animal studies helped people and animals with diabetes?

Prior to the 1920s, type 1/insulin-dependent diabetes was a fatal disease, and treatment of patients with type 2 diabetes was limited to diet.

When appropriate, researchers turn to animals that develop or can be induced to develop conditions mimicking diabetes or its complications¹. These are called **animal models**.

In 1889, Joseph von Mering and Oskar Minkowski² showed that removing the pancreas from the dog produced diabetes. This was the first demonstration of an "antidiabetic" factor produced by the pancreas which enables the body to use blood sugar properly.



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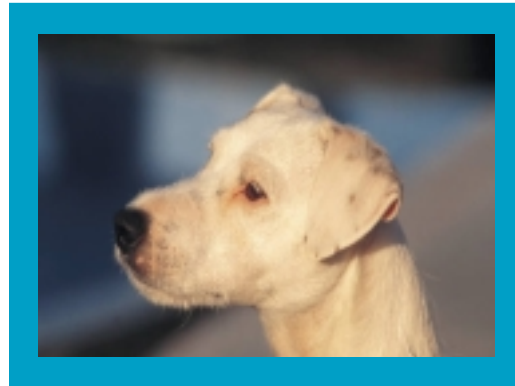
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DIABETES, page 3

Insulin was first extracted from the pancreatic tissue of dogs in 1921 by Canadian physiologists Sir Frederick Banting and Charles Best and British physiologist John MacLeod. Drs. Banting and MacLeod were awarded the Nobel Prize in 1923 for their work.

By 1922, methods for extraction of insulin in pure form from beef pancreas had been developed by Canadian biochemist James Collip. On January 23, 1922, the first successful test of insulin on a human patient with diabetes occurred. Insulin was given to a critically ill patient, whose condition improved dramatically within just a few hours of insulin delivery. Insulin from cow and pig sources then became available for treatment of diabetic patients and was routinely used until the last decade.



Today, insulin can be manufactured using genetic engineering techniques, in which bacteria are made to produce human insulin. The insulin isolated in this fashion is regarded as 100% pure and unlike bovine (cow-based) and porcine (pig-based) insulin, **recombinant human insulin** produces few allergic reactions. Research using dogs and rats led to the development of all types of insulin used today.

Since 1922, diabetes research has utilized a variety of animal models, including rabbits, rats, cows, dogs and sheep. Animal models have aided patients with diabetes in studies on dietary needs. Excellent patient information is available today about dietary management of diabetes, delaying the onset of insulin dependence for many type 2 patients. Nutritional information such as this is available due to controlled experiments in animals.

The monkfish is a deepwater fish weighing up to 70 pounds, with a toothy mouth that can be more than a foot wide. An ichthyologist in the mid-19th century described marble-sized protrusions inside the abdominal cavity of the monkfish, which physiologists recognized as insulin-secreting bodies known as **islets of Langerhans**. While islets in other vertebrate animals are tiny clusters of cells, in the monkfish they are accessible as large formations. One monkfish can yield 20 to 40 times more islet tissue than any other source. Researchers have been able to use this tissue to study how insulin and an insulin regulator called **somatostatin** are produced in islet cells.

Animal models have also been key to the development of oral therapeutic agents, laser treatment for diabetic retinopathy (an eye disease), transplantation of pancreatic tissue, and development of the insulin pump.



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DIABETES, page 4

Insulin-dependent patients with diabetes have been aided by the development of both external and implantable insulin delivery systems. In these devices, a com-



Insulin pump

puterized pump serves as an artificial pancreas that provides insulin to the body at a controlled rate.

These insulin pumps provide precise control of blood sugar levels, without which conditions such as blindness and kidney disease could result. The insulin pump also frees patients from the burden of daily insulin injections. Due to years of careful

evaluation and refinement in dogs, insulin pumps are now available to patients with diabetes.

Until 30 years ago, death of a fetus was 10 to 20 times more common in pregnant women with diabetes. Through animal research, particularly using the rat model, a better understanding of how diabetes influences organ development has led to improved care of pregnant women with diabetes. In women with diabetes today, their risks and the risks to the pregnancy are greatly reduced.

Diabetes complications remain a health threat to diabetic patients. Patients with kidney failure are able to continue their lives through the availability of **dialysis**, which filters and cleanses the blood using a machine. The kidney dialysis machine was developed by Boston area researchers in the early 1950s using dogs.



Kidney Dialysis

Do we still need to use animals in diabetes research?

Today millions of people and animals with diabetes live healthy and longer lives through insulin therapy, oral medications, and other treatments made possible through biomedical research, including the use of animals. Insulin and other therapies are not a cure for diabetes, however. Complications may occur, especially in children, in whom diabetes is the most common chronic disease. Although major advances have been made in the study of diabetes in both people and animals, research still relies on animal models. The inheritance, cause and prevention of diabetes in people and animals are still unsolved problems.

Scientists use rats, rabbits, dogs and nonhuman primates to study long-term complications of diabetes, particularly those involving blood vessels. Studies using diabetic rats have shown how abnormally high blood glucose concentrations alter the function of blood vessels that supply nutrients to various organs, especially the brain. Rats, rabbits, and mice are used to study the effects of partial loss of the insuling-producing islet cells of the pancreas and the mechanism of action of insulin. A rabbit model is leading to insights about how diabetes affects the metabolism of blood fats and the development of atherosclerosis



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DIABETES, page 5

(hardening of the arteries). Dogs are being used as a model for diabetic eye disease. By using animal models to understand the mechanisms of these vascular complications, we may be able to prevent them, or at least to minimize their consequences.

While rodents have been invaluable in the study of diabetes, they have a natural life span of only a few years, making it difficult to study the long-term complications of diabetes. Dogs live about 12 years on average, and often die before complications develop. Rhesus monkeys in captivity that have an unlimited access to food naturally develop a kind of type 2 diabetes similar to that in humans. These primates live 20-30 years, making it possible to study diabetes complications. Primates offer another advantage in studying diabetes. Unlike people, who develop diabetes over a period of 10-30 years, monkeys develop the disease over a 3- to 5-year period. This allows scientists to track every step in the development of the disease and its complications.



Before any real preventive measures can be developed, the exact mechanisms of the immune reaction leading to the development of diabetes must be worked out. The non-obese diabetic mouse (**NOD mouse**) is an animal model used to study the early stages of type 1 diabetes. The immune systems of NOD mice attack their pancreases in a process similar to the autoimmune reaction that causes type 1 diabetes in people. The damaged pancreas from a diabetic mouse contains many types of immune cells, including different types of **T cells**. Scientists are looking, among other things, at which type of T cell is required for the initiation of diabetes.

Animals are also providing insights into the genetics of diabetes. Mice prone to type 1 diabetes have a small mutation in a gene called IDDM18. This produces a chemical, IL-12, that signals to the immune system to attack islet cells.

Families with type 1 diabetes have been shown to have a similar genetic change³. Rats of the strain BB, which naturally develop type 1 diabetes, have a gene, *Ian5*, with a mutation that deletes a protein in various tissues⁴. Researchers have identified a human gene, *SHIP2*, that could predispose people to type 2 diabetes. Mice engineered to lack this gene show that it is a critical and essential regulator of insulin signalling and insulin sensitivity⁵. The *SHIP2* gene is a therapeutic target for the treatment of type 2 diabetes.

What non-animal methods are used in conjunction with animal models in diabetes research?

The Human Genome Project has provided a basic map of the DNA comprising human chromosomes, and the subsequent mapping of other mammalian and non-mammalian animal genomes is providing genomic maps of



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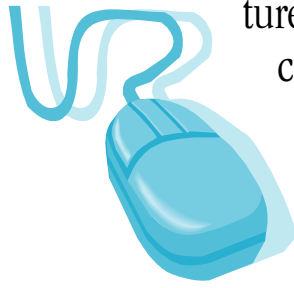
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DIABETES, page 6

other species as well. These maps enable scientists to better understand the genetic basis of disease.

New technologies such as **DNA chips** can be used to determine where and when specific genes on chromosomes are expressed (i.e., when proteins are manufactured from the genes).



Sophisticated computer analysis, a field called **bioinformatics**, makes it possible to examine biological data on a large scale and to gather specific information. With this information, it is possible to make predictions about how complex gene combinations (called genotypes) are related to health or disease. These studies will help us understand not only what goes wrong in diseases such as diabetes, but also provide the capacity to help us avoid disease.

Using these techniques, researchers have recently linked some cases of type 2 diabetes to mutations in the regulatory gene **IDX-1**⁶. Functional analysis of this gene in mice then demonstrated it plays a role in beta cell development and insulin gene activation. Genomic approaches such as this are expected to yield information about other genes linked to diabetes. Once these genes are identified, as with the **IDX-1** gene, their functions must be identified and understood in animal models so that treatments can be designed to target and manipulate them to restore insulin production and insulin sensitivity in diabetic patients.

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What lies ahead for people and animals with diabetes?

New Animal Models

Researchers have developed a fruit fly model with a condition that mimics human diabetes⁷. This model will help shed light on how pancreatic **beta cells** develop. The more scientists understand their normal development, the better chance they will have of making stem cells evolve into insulin-producing cells.

Injection-free Living

Injections could become a thing of the past if another route of insulin delivery can be found. Research is underway on a noninvasive glucose sensor which, combined with an insulin pump, may lead to the development of an artificial pancreas. While insulin is destroyed by digestive juices, encapsulation of oral insulin in biodegradable microspheres has shown some success in rats⁸.

A prototype for an ultrasound insulin delivery system that can be worn as a patch on the body has been developed and is being tested in rats. Medications such as insulin that cannot be taken orally are candidates for administration via this route⁹.

Islet Transplants

Research continues on islet transplantation for treating type 1 diabetes. Islet transplantation is a method of restoring the body's ability to produce



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DIABETES, page 7

insulin by implanting functioning pancreatic islet cells. The supply of islets available from cadaver donors is too limited to help many of the patients in need. Only ~3,000 pancreases become available for transplantation annually, and patients require islets from two pancreases for each transplant procedure.

At this time, investigators are still working out the problems of supply of islet tissue for transplantation, as well as the need for long-term suppression of the immune system with drugs due to tissue rejection. Pig islets have been transplanted into immune-deficient mice and dogs. Rejection has been prevented in dogs by immunosuppressant (immune system-suppressing) drugs. In some experiments, transplantation of islets in rhesus monkeys treated with an experimental immunosuppressant was highly successful; a year after the transplant, it was reported that the monkeys no longer needed insulin injections or immunosuppressants¹⁰.

Scientists have developed a method for pancreatic duct cells, which do not normally produce insulin, to evolve into insulin-producing cells. These cells would normally be discarded in the process of preparing human islet tissue for transplantation¹¹.

Stem Cells

Many scientists believe that stem cell research holds significant potential to help people with a variety of diseases, including type 1 diabetes. The use of stem cells in diabetes research are one way scientists are trying to avoid the issues of tissue rejection and islet tissue shortage.

Stem cells taken from NOD mice have been cultured to produce islet cells, which have been shown experimentally to reverse diabetes when injected back into the mice¹². This discovery, if it is able to be developed, could eventually become a standard of diabetes treatment.

Vaccines

Research into the causes of diabetes has raised the possibility of developing vaccines to retrain the immune system to reset itself. In mice, diabetes is preventable by ridding the pancreas of GAD, a common protein that resides on the walls of pancreatic cells. Gene therapy with the gene that produces GAD also prevented genetically susceptible young mice from becoming diabetic¹³. A further approach has come from a vaccine that resets the natural balance between two kinds of immune cells, Th1 and Th2 cells. Mice given three injections over a two-week period remained diabetes-free for more than a year¹⁴.

Inserting a harmless virus that has been modified to make an insulin-like chemical has been successful in animals. The chemical regulates blood glucose levels but, unlike insulin, does not require high blood glucose levels to become activated¹⁵.



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DIABETES, page 8

Taken together, the available data indicate that some vaccines have a protective effect on the risk of developing diabetes in animals, although more studies are needed to understand these findings and to adapt them for clinical use¹⁶.

Immune System Modification

Research using an animal model such as the NOD mouse is geared toward the prevention of insulin-dependent diabetes. In these mice, something activates the immune system to destroy the islet cells^{17,18,19}.

Preliminary findings have shown that an unexpectedly simple treatment can retrain the immune system to halt destruction of islet cells, curing insulin-dependent diabetes in mice²⁰. Some of the T-cells of diabetic mice do not express self-peptides, which are proteins that tell the immune system not to attack itself, and which are themselves susceptible to attack from the naturally occurring protein, TNF-alpha. By stimulating TNF-alpha production and self-peptide expression, scientists can ensure that newly emerging immune cells do not attack the islet cells²¹. Similarly, diabetes has been prevented in mice genetically prone to it by manipulating iNKT cells in the immune system. These prevent the system from attacking healthy tissue, and are also present in humans, so their discovery could lead to human therapies²².

Viruses and Maternal Antibodies

The autoimmune trigger of type 1 diabetes might be viral infection. Scientists have discovered that the peculiar ability of normal insulin-producing cells to resist infection by coxsackie virus is due to their robust response to natural antiviral compounds called interferons. Mice whose insulin-producing cells were prevented from responding normally to interferons were susceptible to damage by coxsackie virus, and developed acute diabetes similar to that developed by humans after severe viral infection²³.

The seeds of diabetes might rest in antibodies passed from mother to infant. Female mice that had a diabetes-like disease, and were unable to produce antibodies against insulin, produced offspring with reduced rates of the disease. Similar protective effects occurred when researchers implanted diabetes-susceptible mouse embryos into surrogate mothers that were not diabetes-prone²⁴.

Animal-Specific Benefits

Diabetic dogs will soon have their own treatment for diabetes. Vetsulin, the first FDA-approved insulin for canines, will be available in late summer 2004. Prior to the drug's approval, veterinarians had to use human insulin to treat their diabetic canine patients.



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DIABETES, page 9

The dog genome has recently been mapped. In addition to its implications for human health, this development will advance our knowledge of metabolism for the improvement of companion animal nutrition and health.

In one study, dogs are being used to identify biomarkers of canine diabetes. A diet of animal-based ingredients has been compared to a plant-based diet, so that researchers can monitor digestion, fetal microbes and concentrations of fermented end products to measure dietary effects. It is hoped the study will identify molecular markers that can predict diabetes in companion animals. Such studies could result in animal feed that includes functional ingredients to help prevent and/or treat diseases such as diabetes, as well as to target breed-specific conditions.

Application of Diabetes Research to Other Diseases

There is a growing realization among diabetes researchers that the defective immune system T cell thought to cause type 1 diabetes may also cause other autoimmune diseases such as lupus, rheumatoid arthritis and multiple sclerosis. The implications that may emerge from this area of ongoing biomedical research may extend well beyond diabetes alone.



Animal research is critical to the further understanding and treatment of diabetes. If research were stopped, the cost in human and animal suffering and quality of life, as well as the financial burden to our society, would be enormous. Research has already improved the quality and length of life for people and animals with diabetes. With continued biomedical research, including the use of animals, prevention and cure of this debilitating disease are within reach.

GLOSSARY

- Animal model ...** an animal used in research that develops or can be induced to develop conditions mimicking a given disease or condition.
- Autoimmune disease ...** a disease in which the body's immune system mistakenly attacks and destroys certain types of its own normal, healthy cells. In type I diabetes, autoimmunity destroys the beta cells in the pancreas that produce and secrete insulin.
- Beta cell ...** a specialized cell in the pancreatic islets of Langerhans that produces and secretes insulin.
- Bioinformatics ...** a field of biology concerned with the development of techniques for the collection and manipulation of biological data, and the use of such data to make life science discoveries or predictions. The field encompasses computational methods and theories, and generally to computer-based methods for solving biological problems.
- Diabetic retinopathy ...** diabetic eye disease characterized by damage to the small blood vessels in the retina and often resulting in loss of vision.
- Dialysis ...** the process of cleaning wastes from the blood artificially when the kidneys can no longer do the job.



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DIABETES, page 10

- DNA ...** abbreviation for "deoxyribonucleic acid." DNA contains the genetic blueprint for life.
- DNA chips ...** arrays of 10-20,000 gene fragments arranged on the surface of a glass chip. These can be used to identify which genes are expressed at any given time.
- Gene ...** a functional unit of heredity. A segment of DNA located in a specific site on a specific chromosome. A gene directs the production of an enzyme or other protein.
- Glucose ...** one of the simplest forms of sugar. Glucose is the main sugar found in the blood and the body's main source of energy. Cells cannot use glucose without the help of insulin.
- Hormone ...** a chemical produced in one part of the body and released into the blood to trigger or regulate particular functions of the body. For example, insulin is a hormone made in the pancreas that tells other cells when to use glucose for energy.
- Immuno-suppressant ...** a drug that suppresses the body's natural immune responses. Immunosuppressants are given to transplant patients to prevent organ rejection or to patients with autoimmune diseases.
- Insulin ...** a hormone produced by pancreatic beta cells to help glucose enter the body's cells.
- Insulin resistance ...** the phenomenon of poor response to the presence of insulin.
- Islets (of Langerhans) ...** clusters of cells within the pancreas that contain beta cells and other hormone-producing cells. [Pronunciation: EYE-lets]
- NOD mouse ...** non-obese diabetic mouse. A strain of mouse in which the female has an especially high incidence of a diabetes similar to type I diabetes in humans.
- Pancreas ...** an organ that makes insulin and other hormones, and enzymes for digestion. The pancreas is located behind the lower part of the stomach and is about the size of a hand.
- Protein ...** a complex molecule in the body made up of amino acids. Proteins are essential components of all living cells. They provide cell structure and perform the functions of cells. Hormones and enzymes are types of proteins.
- Recombinant human insulin ...** genetically engineered insulin very similar to insulin made by the human body. The DNA code for making human insulin is inserted into bacteria or yeast cells and the insulin made is purified and sold as human insulin.
- Somatostatin ...** a hormone that inhibits the release of growth hormone and controls important physiological functions of the kidney, pancreas and gastrointestinal tract. Somatostatin also acts as a neurotransmitter in the central and peripheral nervous systems.
- Stem cells ...** unspecialized cells which have the ability to divide without limit and develop into many types of differentiated, or specialized, cells.
- T cells ...** specialized cells of the immune system that bind to immune proteins and initiate an immune response when they encounter foreign protein fragments.
- Type I diabetes ...** a type of diabetes in which the insulin-producing beta cells of the pancreas are damaged. People with type I diabetes produce little or no insulin, so glucose cannot get into the body's cells for use as energy. This causes blood glucose to rise. People with type I diabetes must use insulin injections to control their blood glucose.
- Type II diabetes ...** a type of diabetes in which the insulin produced is either not enough or the person's body does not respond normally to the amount present. When there is not enough insulin or the insulin is not used as it should be, glucose cannot get into the body's cells for use as energy. This causes blood glucose to rise.



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DIABETES, page 11

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