1. Introduction to Diabetes

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Diabetes mellitus is characterized by abnormally high levels of sugar (glucose) in the blood.

When the amount of glucose in the blood increases, e.g., after a meal, it triggers the release of the hormone insulin from the pancreas. Insulin stimulates muscle and fat cells to remove glucose from the blood and stimulates the liver to metabolize glucose, causing the blood sugar level to decrease to normal levels [http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View.. ShowSection&rid=mcb.figgrp.5903].

In people with diabetes, blood sugar levels remain high. This may be because insulin is not being produced at all, is not made at sufficient levels, or is not as effective as it should be. The most common forms of diabetes are type 1 diabetes (5%), which is an autoimmune disorder, and type 2 diabetes (95%), which is associated with obesity. Gestational diabetes is a form of diabetes that occurs in pregnancy, and other forms of diabetes are very rare and are caused by a single gene mutation.

For many years, scientists have been searching for clues in our genetic makeup that may explain why some people are more likely to get diabetes than others are. "The Genetic Landscape of Diabetes" introduces some of the genes that have been suggested to play a role in the development of diabetes.

Classification

Diabetes is classified by underlying cause. The categories are: type 1 diabetes—an autoimmune disease in which the body's own immune system attacks the pancreas [http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?tool=bookshelf&call=bv.View..ShowSection&rid=imm.figgrp.1942], rendering it unable to produce insulin; type 2 diabetes—in which a resistance to the effects of insulin or a defect in insulin secretion may be seen; gestational diabetes; and "other types". Table 1 compares the presentation (phenotype) of type 1 and type 2 diabetes.

Table 1. Comparison of Type 1 and Type 2 Diabetes

	Type 1 diabetes	Type 2 diabetes
Phenotype	Onset primarily in childhood and adolescence	Onset predominantly after 40 years of age*
	Often thin or normal weight	Often obese
	Prone to ketoacidosis	No ketoacidosis
	Insulin administration required for survival	Insulin administration not required for survival
	Pancreas is damaged by an autoimmune attack	Pancreas is not damaged by an autoimmune attack
	Absolute insulin deficiency	Relative insulin deficiency and/or insulin resistance
	Treatment: insulin injections	Treatment: (1) healthy diet and increased exercise; (2) hypoglycemic tablets; (3) insulin injections
Genotype	Increased prevalence in relatives	Increased prevalence in relatives
	Identical twin studies: <50% concordance	Identical twin studies: usually above 70% concordance
	HLA association: Yes	HLA association: No

* Type 2 diabetes is increasingly diagnosed in younger patients.

Type 2 diabetes commonly occurs in adults who are obese. There are many underlying factors that contribute to the high blood glucose levels in these individuals. An important factor is the body's resistance to insulin in the body, essentially ignoring its insulin secretions. A second factor is the falling production of insulin by the beta cells of the pancreas. Therefore, an individual with type 2 diabetes may have a combination of deficient secretion and deficient action of insulin.

In contrast to type 2, type 1 diabetes most commonly occurs in children and is a result of the body's immune system attacking and destroying the beta cells. The trigger for this autoimmune attack is not clear, but the result is the end of insulin production.

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History of Diabetes

Physicians have observed the effects of diabetes for thousands of years. For much of this time, little was known about this fatal disease that caused wasting away of the body, extreme thirst, and frequent urination. It wasn't until 1922 that the first patient was successfully treated with insulin.

One of the effects of diabetes is the presence of glucose in the urine (glucosuria). Ancient Hindu writings, many thousands of years old, document how black ants and flies were attracted to the urine of diabetics. The Indian physician Sushruta in 400 B.C. described the sweet taste of urine from affected individuals, and for many centuries to come, the sweet taste of urine was key to diagnosis.

Around 250 B.C., the name "diabetes" was first used. It is a Greek word that means "to syphon", reflecting how diabetes seemed to rapidly drain fluid from the affected individual. The Greek physician Aretaeus noted that as affected individuals wasted away, they passed increasing amounts of urine as if there was "liquefaction of flesh and bones into urine". The complete term "diabetes mellitus" was coined in 1674 by Thomas Willis, personal physician to King Charles II. Mellitus is Latin for honey, which is how Willis described the urine of diabetics ("as if imbued with honey and sugar").

Up until the mid-1800s, the treatments offered for diabetes varied tremendously. Various "fad" diets were prescribed, and the use of opium was suggested, as were bleeding and other therapies. The most successful treatments were starvation diets in which calorie intake was severely restricted. Naturally, this was intolerable for the patient and at best extended life expectancy for a few years.

A breakthrough in the puzzle of diabetes came in 1889. German physicians Joseph von Mering and Oskar Minkowski surgically removed the pancreas from dogs. The dogs immediately developed diabetes. Now that a link was established between the pancreas gland and diabetes, research focused on isolating the pancreatic extract that could treat diabetes.

When Dr. Frederick Banting took up the challenge of isolating a pancreatic extract, he was met with much skepticism. Many great physiologists had tried and failed to isolate an internal secretion from the pancreas. But Banting, a surgeon, persisted and in May 1921, he began work in the laboratory of Professor John Macloed in Toronto, Canada. Charles Best, a medical student at the time, worked as his assistant.

To concentrate what we now know as insulin, Banting tied the pancreatic ducts of dogs. The pancreatic cells that released digestive enzymes (and could also destroy insulin) degenerated, but the cells that secreted insulin were spared. Over several weeks the pancreas degenerated into a residue from which insulin could be extracted. In July 1921, a dog that had had its pancreas surgically removed was injected with an extract collected from a duct-tied dog. In the two hours that followed the injection, the blood sugar level of the dog fell, and its condition improved. Another de-pancreatized (diabetic-like) dog was kept alive for eight days by regular injections until supplies of the extract, at that time called "isletin", were exhausted.

Further experiments on dogs showed that extracts from the pancreas caused a drop in blood sugar, caused glucose in the urine to disappear, and produced a marked improvement in clinical condition. So long as the extract was being given, the dogs were kept alive. The supply of the

extract was improved: the pancreas of different animals were used until that of the cow was settled upon. This extract kept a de-pancreatized dog alive for 70 days. Dr. J. Collip, a biochemist, was drafted to continue improving the purity of the pancreas extract, and later, Best carried on this work.

A young boy, Leonard Thompson, was the first patient to receive insulin treatment. On January 11, 1922, aged 14 and weighing only 64 pounds, he was extremely ill. The first injections of insulin only produced a slight lowering of blood sugar level. The extract still was not pure enough, and abscesses developed at the injection site. Collip continued to refine the extract. Several weeks later, Leonard was treated again and showed a remarkable recovery. His blood sugar levels fell, he gained weight and lived for another 13 years. He died from pneumonia at the age of 27.

During the spring of 1922, Best increased the production of insulin to enable the treatment of diabetic patients coming to the Toronto clinic. Over the next 60 years, insulin was further refined and purified, and long-acting and intermediate types were developed to provide more flexibility. A revolution came with the production of recombinant human DNA insulin in 1978. Instead of collecting insulin from animals, new human insulin could be synthesized.

In 1923, Banting and Macloed were awarded the Nobel Prize for the discovery of insulin. Banting split his prize with Best, and Macloed split his prize with Collip. In his Nobel Lecture, Banting concluded the following about their discovery:

"Insulin is not a cure for diabetes; it is a treatment. It enables the diabetic to burn sufficient carbohydrates, so that proteins and fats may be added to the diet in sufficient quantities to provide energy for the economic burdens of life."

Link Roundup

Discovery of Insulin

Nobel Prize [www.nobel.se/medicine/laureates/1923/index.html] for the discovery of insulin

Development of Insulin [http://digital.library.utoronto.ca/insulin/], University of Toronto

Banting Digital library [http://www.newtecumseth.library.on.ca/banting/], New Tecumseth Public Library, Canada

Discovery of insulin [www.discoveryofinsulin.com/Home.htm]

Epidemiology

Over 18 million Americans have diabetes; of these, about 5 million do not know they have the disease (1).

Type 1 diabetes accounts for 5-10% of cases, affecting 1 of 400 children and adolescents.

Type 2 diabetes is extremely common, accounting for 90-95% of all cases of diabetes. This form of diabetes can go undiagnosed for many years, but the number of cases that are being diagnosed is rising rapidly, leading to reports of a diabetes epidemic.

The Type 2 Diabetes Epidemic

When people think of epidemics, they often think of infectious diseases such as SARS, HIV, or the flu. However, the prevalence of type 2 diabetes is now at epidemic proportions. In the United States, diabetes accounts for over 130 billion dollars of health care costs and is the fifth leading cause of death (2). The number of new cases being diagnosed continues to rise. It has been estimated that of the children born in the year 2000, 1 of 3 will suffer from diabetes at some point in their lifetime (3). Diabetes is predicted to become one of the most common diseases in the world within a couple of decades, affecting at least half a billion people (4).

Estimate your risk of developing Type 2 Diabetes [www.healthcalculators.org/calculators/diabetes.asp]

In the past, type 2 was rarely seen in the young, hence its original name of "adult-onset diabetes". But now type 2 diabetes is increasingly being diagnosed in young adults and even in children. In Japan, more children suffer from type 2 than type 1 ("juvenile onset") diabetes. This young generation of diabetics will have many decades in which to develop the complications of diabetes.

In 1990, 4.9% of the American population were diagnosed with diabetes (see Flash Animation 1). This increased to 7.9% by the year 2001 (5).

Obesity

The driving force behind the high prevalence of diabetes is the rise of obesity [http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View..ShowTOC&rid=obesity.TOC] in the population. In today's society, it can be difficult to maintain a healthy weight. We have the combination of ample food and a sedentary lifestyle. This is in stark contrast to only a couple of hundred years ago, when people were more active and food supplies were not as abundant. As a result, many of us are heavier than we should be.

Calculate your ideal weight [www.drkoop.com/template.asp?page=ibw&ap=93]

Being overweight or obese is defined by a calculation called the Body Mass Index (BMI). It is a calculation that takes your height and weight into consideration and gives you a score. A score of 18–24.9 is a healthy weight. If you are overweight, your score lies within the range to 25–29.9; a score of 30 and above indicates obesity.

Calculate your BMI [http://nhlbisupport.com/bmi/bmicalc.htm]

In 1991, it was estimated that 12% of the population were obese (5). By the year 2001, this had increased to an estimated 20.9% of the population; this represents over 44 million obese adult Americans. A more recent study estimated that a record 30% of the American population are now obese (6) (see Flash Animation 2).

Obesity is a major problem for the United states. Every year, an estimated 300,000 US adults die of causes related to obesity (7). Obesity is also a huge economic burden, accounting for up to 4% of healthcare costs in the United States (8).

Thrifty Genes

Epidemics of infectious diseases increase when there is increased spread of the infectious agent and decrease when the number of victims who are susceptible falls (they either become immune or they die). An epidemic of a genetic disease such as type 2 diabetes is similar. The number of cases rises when there is a rise in environmental risk (abundant food supplies, lack of activity) and decreases when the number of susceptible individuals falls (by deaths from the complications of diabetes).

The classic example of an epidemic of diabetes is found on an remote island in the Pacific Ocean, the island of Nauru. Before the turn of the 20th century, the lifestyle of Nauruans was harsh. The soil was poor, agriculture was difficult, and frequent episodes of starvation were common. Despite these adverse conditions, the islanders were noted to be "heavy". In 1922, it was discovered that Nauru contained phosphate rock, which was then mined for use in fertilizer, and for which the islanders received royalties. Over several decades, the Nauruans became extremely wealthy, and with their new-found riches came major lifestyle changes. Food was now abundant and could be bought from stores. Instead of fishing and farming, Nauruans now led sedentary lives. By the 1950s, type 2 diabetes exploded from being non-existent in this population to affecting 2 of 3 adults over the age of 55 and becoming a common cause of death.

The case of the Nauruans is an extreme case of how type 2 diabetes can rapidly reach epidemic proportions, and "thrifty genes" may be involved. It has been postulated by Neel (9) that genes that are metabolically thrifty give a survival advantage in times when there is a constant threat of famine and starvation. When food is abundant, these genes aid the efficient metabolism of the food, enabling rapid build up of fat stores. This enabled people like the Nauruans to survive food shortages later on. But when food is always abundant, a thrifty genetic makeup turns into a survival disadvantage. Thrifty genes cause obesity, which in turn predisposes to diabetes. The epidemic that took hold of the island of Nauru is now emerging in developing countries and already has a firm hold on the developed world.

References

1. National Diabetes Statistics fact sheet: general information and national estimates on diabetes in the United States. National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. U.S. Department of Health and Human Services.

2. Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the US in 2002. Diabetes Care 26(3):917–932; 2003. (PubMed)

3. Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime risk for diabetes mellitus in the United States. JAMA 290(14):1884–1890; 2003. (PubMed)

4. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 21(9):1414–1431; 1998. (PubMed)

5. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 289(1):76–79; 2001. (PubMed)

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9. Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? JAMA 14:353–362; 1962. (PubMed)

Box 1: Increase of diabetes in adults in the United States.

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Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 289(1):76–79; 2001. (PubMed)

   To view this you will need to have Flash [http://www.macromedia.com/go/getflashplayer] installed on your computer.

Box 2: Rise of obesity in the United States.

References

Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 289(1):76–79; 2001. (PubMed)

   To view this you will need to have Flash [http://www.macromedia.com/go/getflashplayer] installed on your computer.

Link Roundup

Calculators

   Diabetes Type 2 Risk Calculator [www.healthcalculators.org/calculators/diabetes.asp], University of Maryland Medical Center.

   Calculate your ideal weight [www.drkoop.com/template.asp?page=ibw&ap=93], according to Dr. Koop.

   Calculate your BMI [nhlbisupport.com/bmi/bmicalc.htm] at the National Heart, Lung, and Blood Institute.

Healthy Living

   The DASH diet [www.nhlbi.nih.gov/health/public/heart/hbp/dash/], National Heart, Lung, and Blood Institute.

   Advice from the Obesity Education Initiative [www.nhlbi.nih.gov/about/oei/index.htm], National Heart, Lung, and Blood Institute.

   The President's challenge [www.presidentschallenge.org/].

   Advice from the Surgeon General [www.surgeongeneral.gov/topics/obesity/calltoaction/fact_whatcanyoudo.htm].

Physiology and Biochemistry of Sugar Regulation

Overview of Glucose Metabolism

Glucose is an essential fuel for the body (Figure 1).The amount of glucose in the bloodstream is regulated by many hormones, the most important being insulin.

Insulin is the "hormone of plenty"—it is released when glucose is abundant and stimulates the following:

- muscle and fat cells to remove glucose from the blood

- cells to breakdown glucose, releasing its energy in the form of ATP (via glycolysis and the citric acid cycle)

- the liver and muscle to store glucose as glycogen (short-term energy reserve)

- adipose tissue to store glucose as fat (long-term energy reserve)

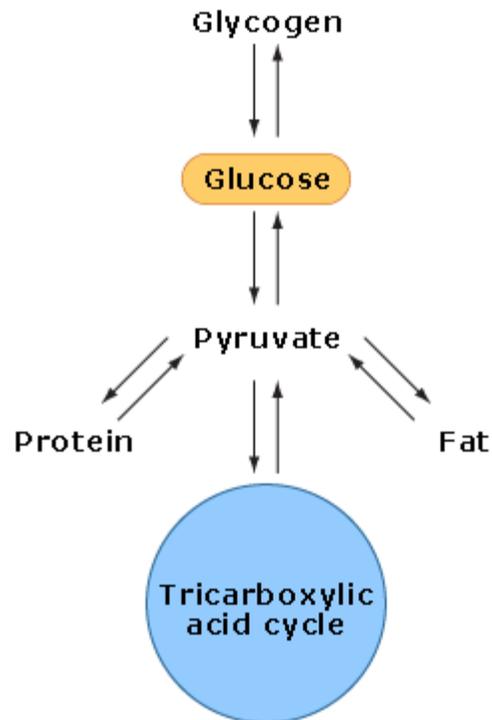- cells to use glucose in protein synthesis

Figure 1: Overview of glucose metabolism.
Glucose is used for many purposes in the body. It can be converted into energy via pyruvate and the tricarboxylic acid (TCA) cycle, as well as being converted to fat (long-term storage) and glycogen (short-term storage). Some amino acids may also be synthesized directly from pyruvate; thus, glucose may also indirectly contribute to protein synthesis.

Glucagon is the main hormone opposing the action [http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?tool=bookshelf&call=bv.View..ShowSection&rid=mcb.figgrp.5903] of insulin and is released when food is scarce. Whereas insulin triggers the formation of glycogen (an energy-requiring process, or an anabolic effect), glucagon triggers glycogen breakdown, which releases energy (a catabolic effect). Glucagon also helps the body to switch to using resources other than glucose, such as fat and protein (Figure 2).
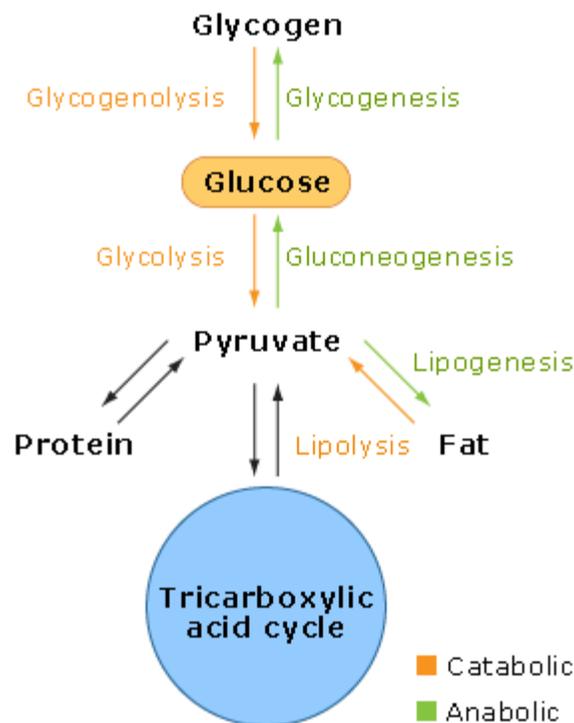
Figure 2: Anabolism and catabolism of glucose.
Glucose metabolism involves both energy-producing (catabolic, shown in orange) and energy-consuming (anabolic, shown in green) processes.

Regulation of Blood Glucose

Blood glucose levels are not constant—they rise and fall depending on the body's needs, regulated by hormones. This results in glucose levels normally ranging from 70 to 110 mg/dl.

The blood glucose level can rise for three reasons: diet, breakdown of glycogen, or through hepatic synthesis of glucose.

Eating produces a rise in blood glucose, the extent of which depends on a number of factors such as the amount and the type of carbohydrate eaten (i.e., the glycemic index), the rate of digestion, and the rate of absorption. Because glucose is a polar molecule, its absorption across the hydrophobic gut wall requires specialized glucose transporters (GLUTS) [http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View..ShowSection&rid=endocrin.box.54] of which there are five types. In the gut, GLUT2 and GLUT5 [http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View..ShowSection&rid=endocrin.box.53] are the most common.

The liver is a major producer of glucose—it releases glucose from the breakdown of glycogen and also makes glucose from intermediates of carbohydrate, protein, and fat metabolism. The liver is also a major consumer of glucose and can buffer glucose levels (see Box 1). It receives glucose-rich blood directly from the digestive tract via the portal vein (Figure 3). The liver quickly removes large amounts of glucose from the circulation so that even after a meal, the blood glucose levels rarely rise above 110 mg/dl in a non-diabetic.
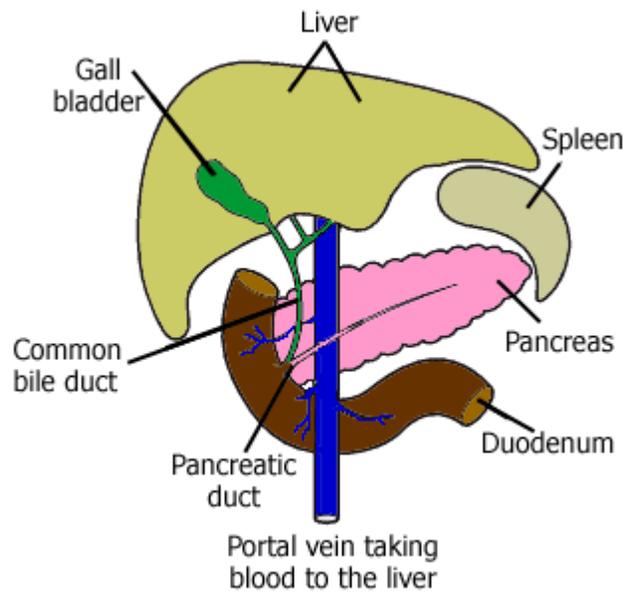
Figure 3: The portal circulation.

The portal vein drains almost all of the blood from the digestive tract and empties directly into the liver. This circulation of nutrient-rich blood between the gut and liver is called the portal circulation. It enables the liver to remove any harmful substances that may have been digested before the blood enters the main blood circulation around the body—the systemic circulation.

After a Meal—the Role of Insulin

The rise in blood glucose following a meal is detected by the pancreatic beta cells, which respond by releasing insulin. Insulin increases the uptake and use of glucose by tissues such as skeletal muscle and fat cells. This rise in glucose also inhibits the release of glucagon, inhibiting the production of glucose from other sources, e.g., glycogen break down (Figure 4).
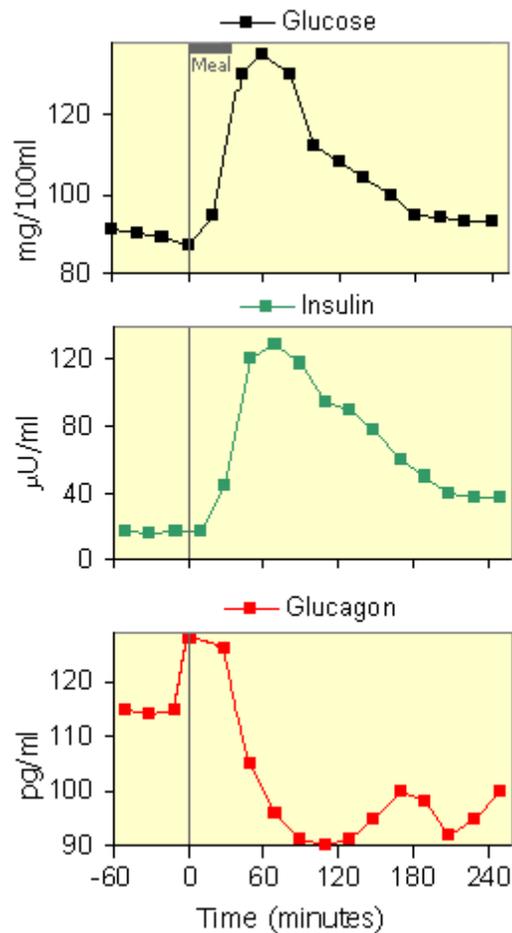
Figure 4: Changes in key hormones after a meal.
Changes in blood levels of glucose, insulin, and glucagon after a carbohyrate-rich meal (ingested at time 0 minutes).

1. Use Glucose

Once inside the cell, some of the glucose is used immediately via glycolysis. This is a central pathway of carbohydrate metabolism because it occurs in all cells in the body, and because all sugars can be converted into glucose and enter this pathway. During the well-fed state, the high levels of insulin and low levels of glucagon stimulate glycolysis, which releases energy and produces carbohydrate intermediates that can be used in other metabolic pathways.

Glycolysis [http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View..ShowSection&rid=stryer.section.2206] in Stryer's *Biochemistry*

2. Make Glycogen

Any glucose that is not used immediately is taken up by the liver and muscle where it can be converted into glycogen [http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View.. ShowSection&rid=stryer.chapter.2911] (glycogenesis). Insulin stimulates glycogenesis in the liver by:

- stimulating hepatic glycogen synthetase (the enzyme that catalyzes glycogen synthesis in the liver)

- inhibiting hepatic glycogen phosphorylase (the enzyme that catalyzes glycogen breakdown in the liver)

- inhibiting glucose synthesis from other sources (inhibits gluconeogenesis)

Insulin also encourages glycogen formation in muscle, but by a different method. Here it increases the number of glucose transporters (GLUT4) on the cell surface. This leads to a rapid uptake of glucose that is converted into muscle glycogen.

Glycogen metabolism [http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View..ShowSection&rid=stryer. chapter.2911] in Stryer's *Biochemistry*

3. Make Fat

When glycogen stores are fully replenished, excess glucose is converted into fat in a process called lipogenesis. Glucose is converted into fatty acids that are stored as triglycerides (three fatty acid molecules attached to one glycerol molecule) for storage. Insulin promotes lipogenesis by:

- increasing the number of glucose transporters (GLUT4) expressed on the surface of the fat cell, causing a rapid uptake of glucose

- increasing lipoprotein lipase activity, which frees up more fatty acids for triglyceride synthesis

In addition to promoting fat synthesis, insulin also inhibits fat breakdown [http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View..ShowSection&rid=stryer.chapter.3038] by inhibiting hormone-sensitive lipase (an enzyme that breaks down fat stores). As a result, there are lower levels of fatty acids in the blood stream.

Fatty acid metabolism [http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?call=bv.View..ShowSection&rid=stryer. chapter.3038] in Stryer's *Biochemistry*

Insulin also has an anabolic effect on protein metabolism. It stimulates the entry of amino acids into cells and stimulates protein production from amino acids.

Fasting—the Role of Glucagon

Fasting is defined as more than eight hours without food. The resulting fall in blood sugar levels inhibits insulin secretion and stimulates glucagon release. Glucagon opposes many actions of insulin. Most importantly, glucagon raises blood sugar levels by stimulating the mobilization of glycogen stores in the liver, providing a rapid burst of glucose. In 10–18 hours, the glycogen

stores are depleted, and if fasting continues, glucagon continues to stimulate glucose production by favoring the hepatic uptake of amino acids, the carbon skeletons of which are used to make glucose.

In addition to low blood glucose levels, many other stimuli stimulate glucagon release including eating a protein-rich meal (the presence of amino acids in the stomach stimulates the release of both insulin and glucagon, glucagon prevents hypoglycemia that could result from unopposed insulin) and stress (the body anticipates an increased glucose demand in times of stress).

Starvation

The metabolic state of starvation in the USA is more commonly found in people trying to lose weight rapidly or in those who are too unwell to eat. After a couple of days without food, the liver will have exhausted its stores of glycogen but continues to make glucose from protein (amino acids) and fat (glycerol).

The metabolism of fatty acids (from adipose tissue) is a major source of energy for organs such as the liver. Fatty acids are broken down to acetyl-CoA, which is channeled into the citric acid cycle and generates ATP. As starvation continues, the levels of acetyl-CoA increase until the oxidative capacity of the citric acid cycle is exceeded. The liver processes these excess fatty acids into ketone bodies (3-hydroxybutyrate) to be used by many tissues as an energy source.

The most important organ that relies on ketone production is the brain because it is unable to metabolize fatty acids. During the first few days of starvation, the brain uses glucose as a fuel. If starvation continues for more than two weeks, the level of circulating ketone bodies is high enough to be used by the brain. This slows down the need for glucose production from amino acid skeletons, thus slowing down the loss of essential proteins.

"Starvation in the Midst of Plenty"

Diabetes is often referred to as "starvation in the midst of plenty" because the intracellular levels of glucose are low, although the extracellular levels may be extremely high.

As in starvation, type 1 diabetics use non-glucose sources of energy, such as fatty acids and ketone bodies, in their peripheral tissues. But in contrast to the starvation state, the production of ketone bodies can spiral out of control. Because the ketones are weak acids, they acidify the blood. The result is the metabolic state of diabetic ketoacidosis (DKA). Hyperglycemia and ketoacidosis are the hallmark of type 1 diabetes (Figure 5).

Hypertriglyceridemia is also seen in DKA. The liver combines triglycerol with protein to form very low density lipoprotein (VLDL). It then releases VLDL into the blood. In diabetics, the enzyme that normally degrades lipoproteins (lipoprotein lipase) is inhibited by the low level of insulin and the high level of glucagon. As a result, the levels of VLDL and chylomicrons (made from lipid from the diet) are high in DKA.
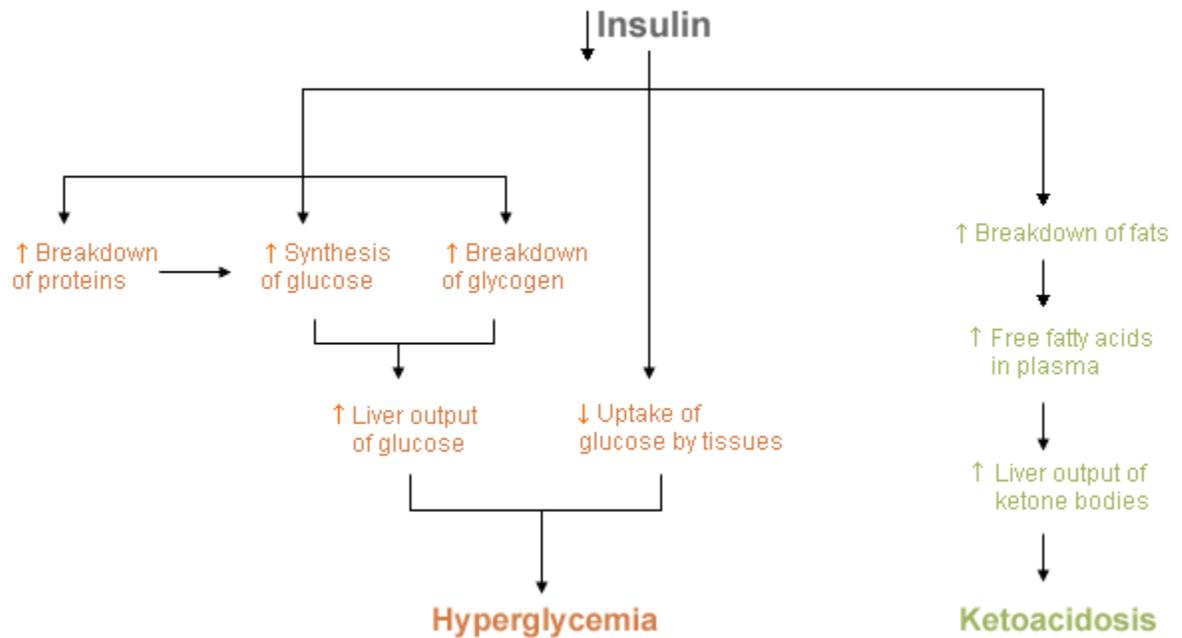
Figure 5: **Metabolic changes in diabetic ketoacidosis.**
Hyperglycemia is caused by the increased production of glucose by the liver (driven by glucagon) and the decreased use of glucose of insulin by peripheral tissues (because of the lack of insulin).

Low-Carbohydrate Diet

Low-carbohydrate diets, such as the "Atkins" and "South Beach" diets, are currently popular ways to lose weight. Such diet plans involve restricting the type and amount of carbohydrate eaten.

One of the earliest descriptions of a low-carbohydrate diet was by William Banting in the 1860s in England. At the age of 66, Banting found success in following a carbohydrate-restricted diet: in the course of one year, he lost 46 pounds of his initial weight of 202 pounds. His impression was that "any starchy or saccharine matter tends to the disease of corpulence in advanced life". He claimed he was never hungry and that "the great charms and comfort of the system are that its effects are palpable within a week of trial and creates a natural stimulus to persevere for a few weeks more".

In a recent small trial, 63 obese men and women were assigned to either a low-carbohydrate diet or a low-fat diet (1). People on both diets lost weight. The carbohydrate-restricted group initially lost weight at a faster rate, but when reviewed at the end of the year there was no significant difference in weight loss between the two groups (1). It was found that low-carbohydrate dieters (who were allowed unrestricted amounts of protein and fat) actually had a lower energy intake than the low-fat diets (who were limited in their calorie intake). It may be that when carbohydrates are restricted, weight loss is due to a lower calorie intake due to the monotony of the diet. It is also possible that the lower calorie intake may be because of a change in peripheral or central saiety signals, leaving people feeling more full after a meal.

A second study compared the effects of a carbohydrate-restricted diet on the risk of developing atherosclerosis (2). 132 severely obese men and women were assigned to either a low-carbohydrate or low-fat diet. Again, after a 6-month period both groups lost weight. They became

more sensitive to insulin, and their triglyceride (TG) levels, a type of fat that is a risk factor for atherosclerosis, improved. However, the carbohydrate-restricted group lost more weight and showed a greater improvement in insulin sensitivity and TG levels. After one year, the weight loss between the two groups was similar, but the cardiogenic risk factors were improved in the low-carbohydrate dieters, TG levels were lower, and levels of HDL cholesterol, a type of fat that protects against atherosclerosis, were higher (3). Also, long-term sugar control, which can be measured by checking for the amount of glycosylated hemoglobin (HbA1c), was better in people on the low-carbohydrate diet. However, it remains unclear whether these beneficial effects would continue after 1 year.

At present, the risks of obesity are well known, and the benefits of weight loss by traditional low-calorie, low-fat, and high-complex carbohydrate diets are also well documented. Future research will clarify the long-term outcomes of a low-carbohydrate diet for achieving and main-taing a healthy weight together with the effects on the heart and other systems of the body.

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Box 1: The liver buffers glucose levels.

- The liver receives glucose-rich blood from the digestive tract via the portal vein (Figure 3).

- The liver has a high amount of GLUT2 transporters that do not need the presence of insulin to transport glucose into the liver cells. GLUT2 has a low affinity for glucose which enables a rapid influx of glucose when sugar levels are high. Therefore, in the liver, levels of glucose inside and outside the cell can become equal (an equilibrium is reached).

- The first step for trapping glucose inside the cell involves phosphorylation to produce glucose-6-phosphate (G6P). The liver differs from the rest of the body in that it uses the enzyme glucokinase, rather than hexokinase. Glucokinase can produce G6P at a faster rate and also is not inhibited by its product (this is because in the liver, G6P can be channeled into making glycogen).

- Glucose and insulin both modulate metabolic enzymes in such a way that glycogen formation is promoted. This drives forward the process of bringing more glucose into the liver. Insulin promotes glycogen synthesis by stimulating glycogen synthetase and inhibiting glycogen phosphorylase.

Link Roundup

The glycemic index [www.joslin.harvard.edu/education/library/glycemic_index.shtml], Joslin Diabetes Center, Boston.

The Story of Insulin

Insulin Synthesis

The insulin-making cells of the body are called beta cells, and they are found in the pancreas gland. These cells clump together to form the "islets of Langerhans", named for the German medical student who described them.

The synthesis of insulin begins at the translation of the insulin gene, which resides on chromosome 11. During translation, two introns are spliced out of the mRNA product, which encodes a protein of 110 amino acids in length. This primary translation product is called preproinsulin and is inactive. It contains a signal peptide of 24 amino acids in length, which is required for the protein to cross the cell membrane.

Once the preproinsulin reaches the endoplasmic reticulum, a protease cleaves off the signal peptide to create proinsulin. Proinsulin consists of three domains: an amino-terminal B chain, a carboxyl-terminal A chain, and a connecting peptide in the middle known as the C-peptide.

Within the endoplasmic reticulum, proinsulin is exposed to several specific peptidases that remove the C-peptide and generate the mature and active form of insulin. In the Golgi apparatus, insulin and free C-peptide are packaged into secretory granules, which accumulate in the cytoplasm of the beta cells. Exocytosis of the granules is triggered by the entry of glucose into the beta cells. The secretion of insulin has a broad impact on metabolism.

Insulin Structure

In 1958, Frederick Sanger was awarded his first Nobel Prize [http://www.nobel.se/chemistry/laureates/1958/] for determining the sequence of the amino acids that make up insulin. This marked the first time that a protein had had the order of its amino acids (the primary sequence) determined.

Insulin is composed of two chains of amino acids named chain A (21 amino acids) and chain B (30 amino acids) that are linked together by two disulfide bridges. There is a 3rd disulfide bridge within the A chain that links the 6th and 11th residues of the A chain together.

In most species, the length and amino acid compositions of chains A and B are similar, and the positions of the three disulfide bonds are highly conserved. For this reason, pig insulin can be used to replace deficient human insulin levels in diabetes patients. Today, porcine insulin has largely been replaced by the mass production of human proinsulin by bacteria (recombinant insulin).

Insulin molecules have a tendency to form dimers in solution, and in the presence of zinc ions, insulin dimers associate into hexamers. Whereas monomers of insulin readily diffuse through the blood and have a rapid effect, hexamers diffuse slowly and have a delayed onset of action. In the design of recombinant insulin, the structure of insulin can be modified in a way that reduces the tendency of the insulin molecule to form dimers and hexamers but that does not interrupt binding to the insulin receptor. In this way, a range of preparations of insulin is made, varying from short acting to long acting.

Insulin secretion

Rising levels of glucose inside the pancreatic beta cells trigger the release of insulin:
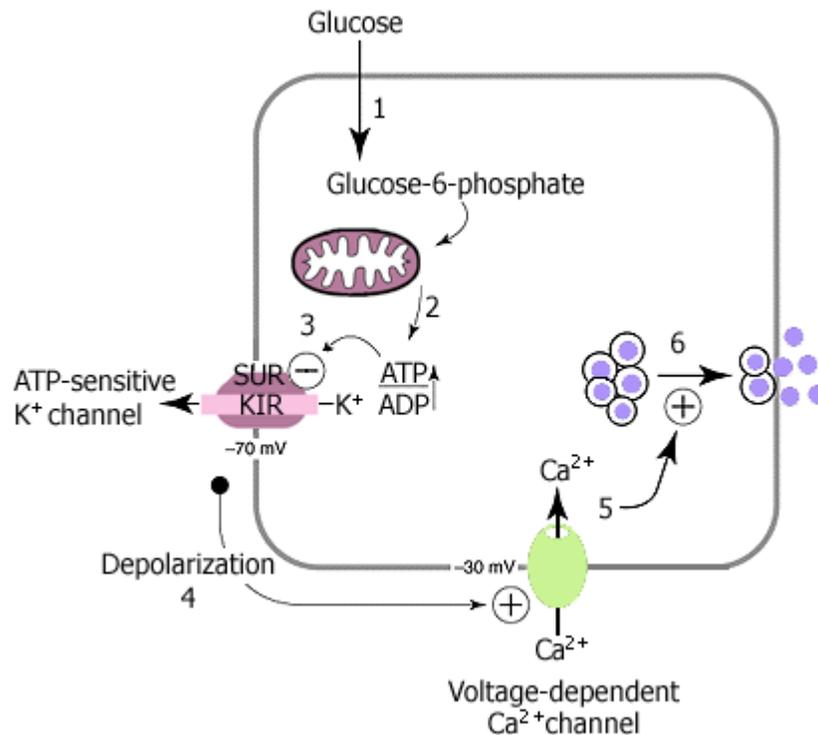
1. Glucose is transported into the beta cell by type 2 glucose transporters (GLUT2). Once inside, the first step in glucose metabolism is the phosphorylation of glucose to produce glucose-6-phosphate. This step is catalyzed by glucokinase—it is the rate-limiting step in glycolysis, and it effectively traps glucose inside the cell.

2. As glucose metabolism proceeds, ATP is produced in the mitochondria.

3. The increase in the ATP:ADP ratio closes ATP-gated potassium channels in the beta cell membrane. Positively charged potassium ions (K^+) are now prevented from leaving the beta cell.

4. The rise in positive charge inside the beta cell causes depolarization.

5. Voltage-gated calcium channels open, allowing calcium ions (Ca^{2+}) to flood into the cell.

6. The increase in intracellular calcium concentration triggers the secretion of insulin via exocytosis.

There are two phases of insulin release in response to a rise in glucose. The first is an immediate release of insulin. This is attributable to the release of preformed insulin, which is stored in secretory granules. After a short delay, there is a second, more prolonged release of newly synthesized insulin.

Once released, insulin is active for a only a brief time before it is degraded by enzymes. Insulinase found in the liver and kidneys breaks down insulin circulating in the plasma, and as a result, insulin has a half-life of only about 6 minutes. This short duration of action allows rapid changes in the circulating levels of insulin.

Insulin Receptor

The net effect of insulin binding is to trigger a cascade of phosphorylation and dephosphorylation reactions. These actions are terminated by dephosphorylation of the insulin receptor.

Similar to the receptors for other polypeptide hormones, the receptor for insulin is embedded in the plasma membrane and is composed of a pair of alpha subunits and a pair of beta subunits (Figure 1). The alpha subunits are extracellular and contain the insulin-binding site. The beta subunits span the membrane and contain the enzyme tyrosine kinase. Kinases are a group of enzymes that phosphorylate proteins (the reverse reaction is catalyzed by a group of enzymes called phosphatases).
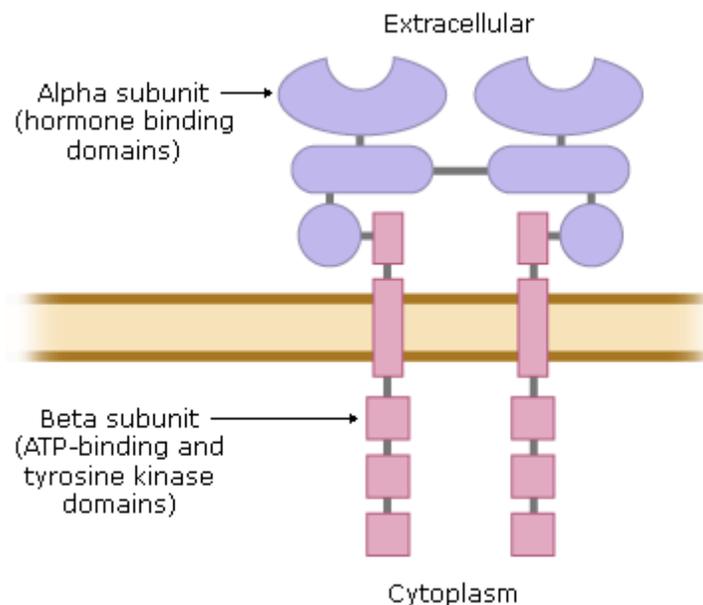

Figure 1: The insulin receptor.
The insulin receptor is a tyrosine kinase receptor and is composed of a pair of alpha subunits and a pair of beta subunits. Insulin binds to the alpha subunits and induces a conformational change that is transmitted to the beta subunits that autophosphorylate and initiate a cascade of phosphorylation and dephosphorylation reactions.

Insulin binding to the alpha subunits induces a conformational change that is transmitted to the beta subunits and causes them to phosphorylate themselves (autophosphorylation). A specific tyrosine of each beta subunit is phosphorylated along with other target proteins, such as insulin receptor substrate (IRS). As these and other proteins inside the cell are phosphorylated, this in turn alters their activity, bringing about the wide biological effects of insulin.

Insulin Action

The binding of insulin results in a wide range of actions that take place over different periods of time.

Almost immediately, insulin promotes the uptake of glucose into many tissues that express GLUT4 glucose transporters, such as skeletal muscle and fat. Insulin increases the the activity of these transporters and increases their numbers by stimulating their recruitment from an intracellu-

lar pool to the cell surface. Not all tissues require insulin for glucose uptake. Tissues such as liver cells, red blood cells, the gut mucosa, the kidneys, and cells of the nervous system use a glucose transporter that is not insulin dependent.

Over minutes to hours, insulin alters the activity of various enzymes as a result of changes in their phosphorylation status.

Over a period of days, insulin increases the amounts of many metabolic enzymes. These reflect an increase in gene transcription, mRNA, and enzyme synthesis.

Link Roundup

Read more about Insulin on the Bookshelf

In Human Molecular Genetics 2, see the post-translation processing [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View.. ShowSection&rid=hmg.figgrp.50] and the primary structure [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View.. ShowSection&rid=hmg.figgrp.51] of insulin.

In Stryer's Biochemistry, read about the receptors that contain tyrosine kinase domains [http://www.ncbi.nlm.nih.gov/books/bv.fcgi? call=bv.View..ShowSection&rid=stryer.section.2093#2101] | See the release of insulin [http://www.ncbi.nlm.nih.gov/books/bv.fcgi? call=bv.View..ShowSection&rid=stryer.figgrp.4354], insulin crystals [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View.. ShowSection&rid=stryer.figgrp.288], and the synthesis of proinsulin by bacteria [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv. View..ShowSection&rid=stryer.figgrp.828].