

The Amazing Story of Diabetes Mellitus

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Outline of the “Amazing Story of Diabetes Mellitus”

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3. *Signs and symptoms of diabetes*
4. *Type 1 diabetes versus Type 2 diabetes*
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 - c. *Pancreas and Islet cell transplants*
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 - e. *Treatment Options In Obesity*
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Ancient History of Diabetes

Diabetes has been known for over 3000 years

(Perhaps only leprosy was described earlier)

The first known mention of diabetes symptoms was in 1552 B.C., when Hesy-Ra, an Egyptian physician noted that ants seemed to be attracted to the urine of people who had this disease.

In 150 AD, the Greek physician Arateus described what we now call diabetes as "the melting down of flesh and limbs into urine."

Centuries later, people known as "water tasters" diagnosed diabetes by tasting the urine of people suspected to have it.
If urine tasted sweet, diabetes was diagnosed.

To acknowledge this feature, in 1675 the word "mellitus," meaning honey, was added to the name "diabetes," meaning siphon.

It wasn't until the 1800s that scientists developed chemical tests to detect the presence of sugar in the urine

Role of the Pancreas in Glucose Utilization

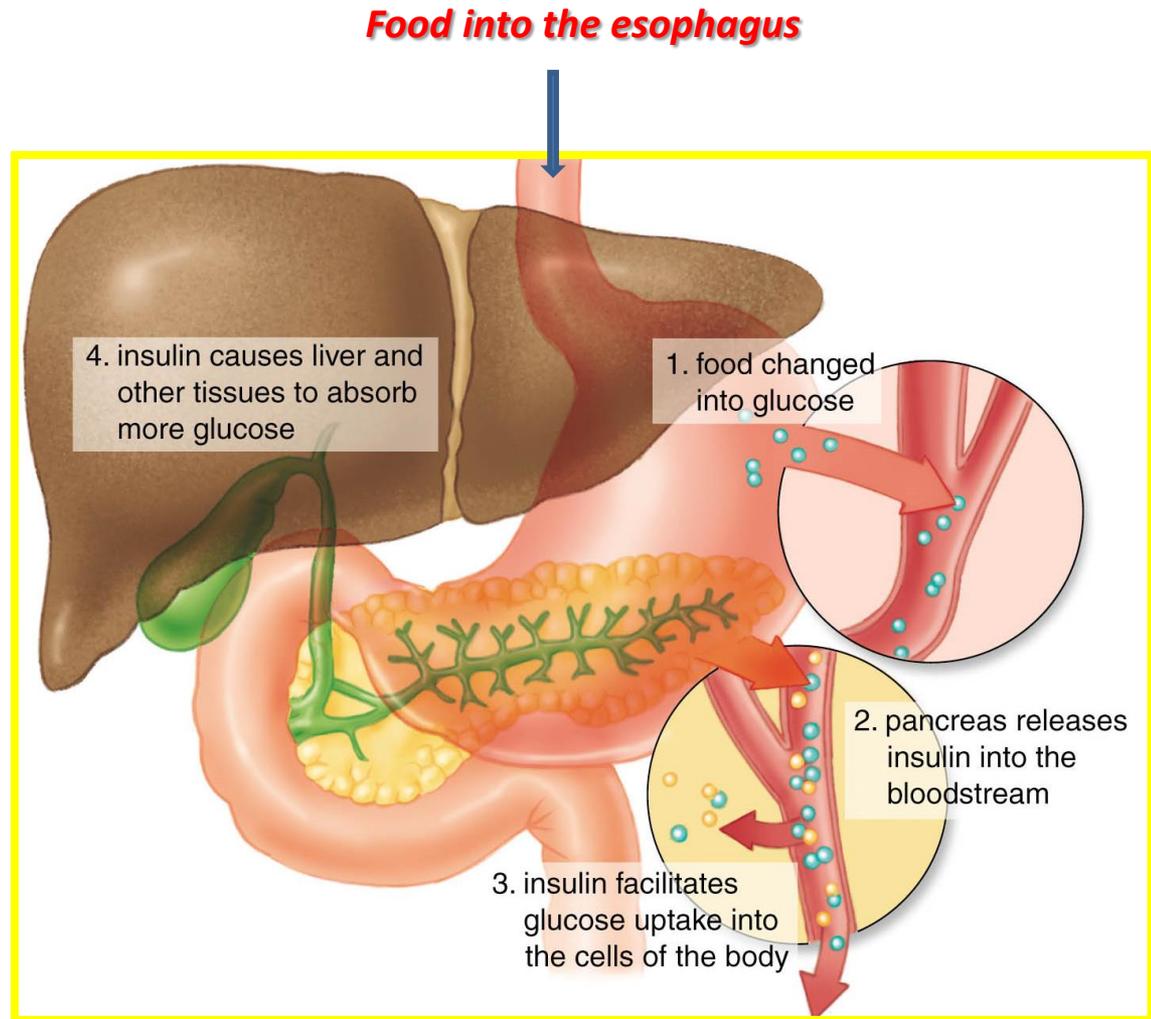
Beta islet cells of pancreas produce insulin which is released in response to a rise in blood glucose allowing glucose to enter cells thus lowering the blood sugar level

Alpha islet cells of pancreas produce glucagon which activates liver cells to break down stored glycogen the storage form of glucose, and release it into the blood to raise blood glucose levels and to facilitate breakdown of fats and proteins into glucose

Overview of Glucose Metabolism

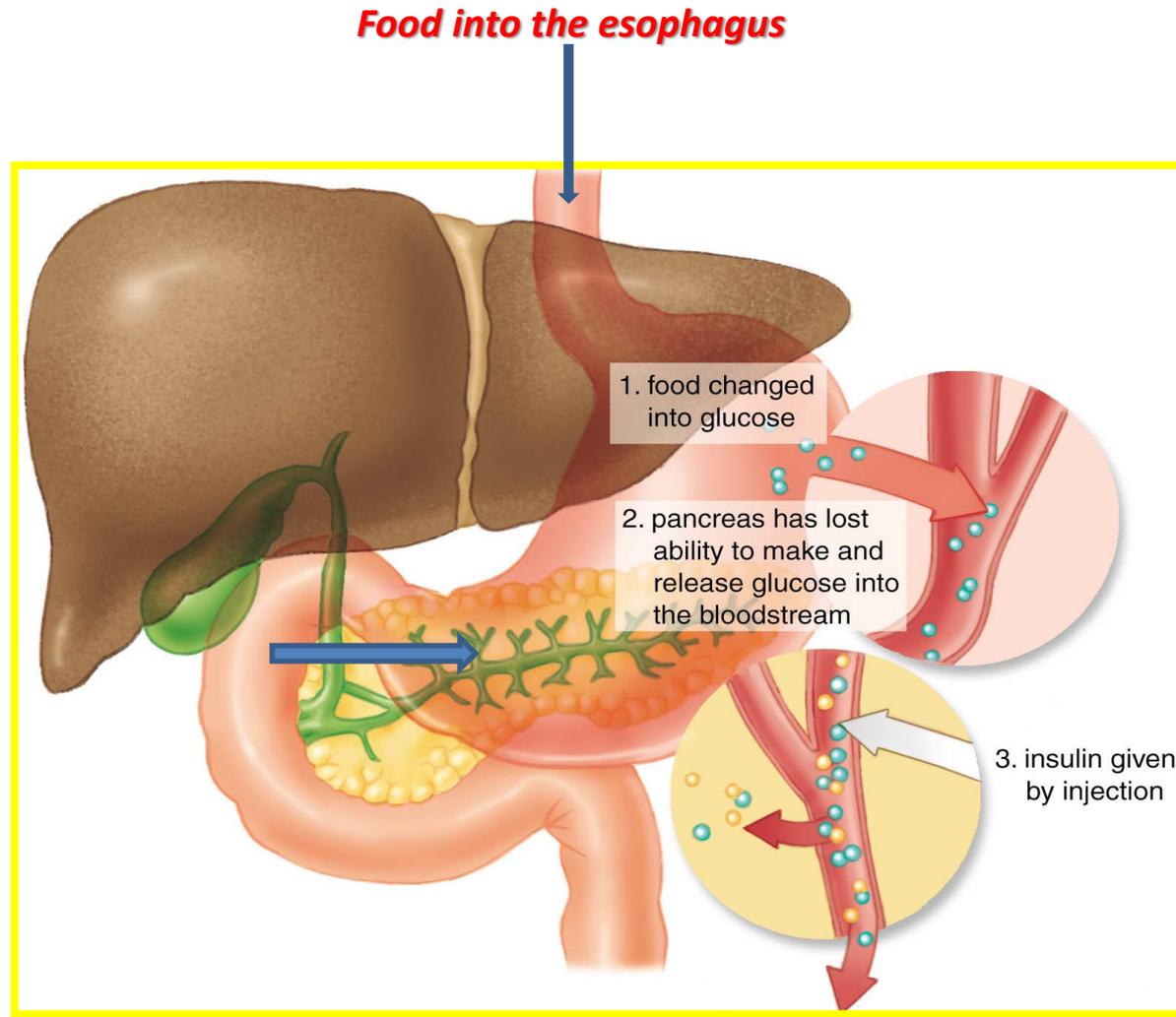
The pancreas releases insulin after eating to lower blood glucose

Glucose that is not used by muscle, brain and other organs is stored in the liver as glycogen



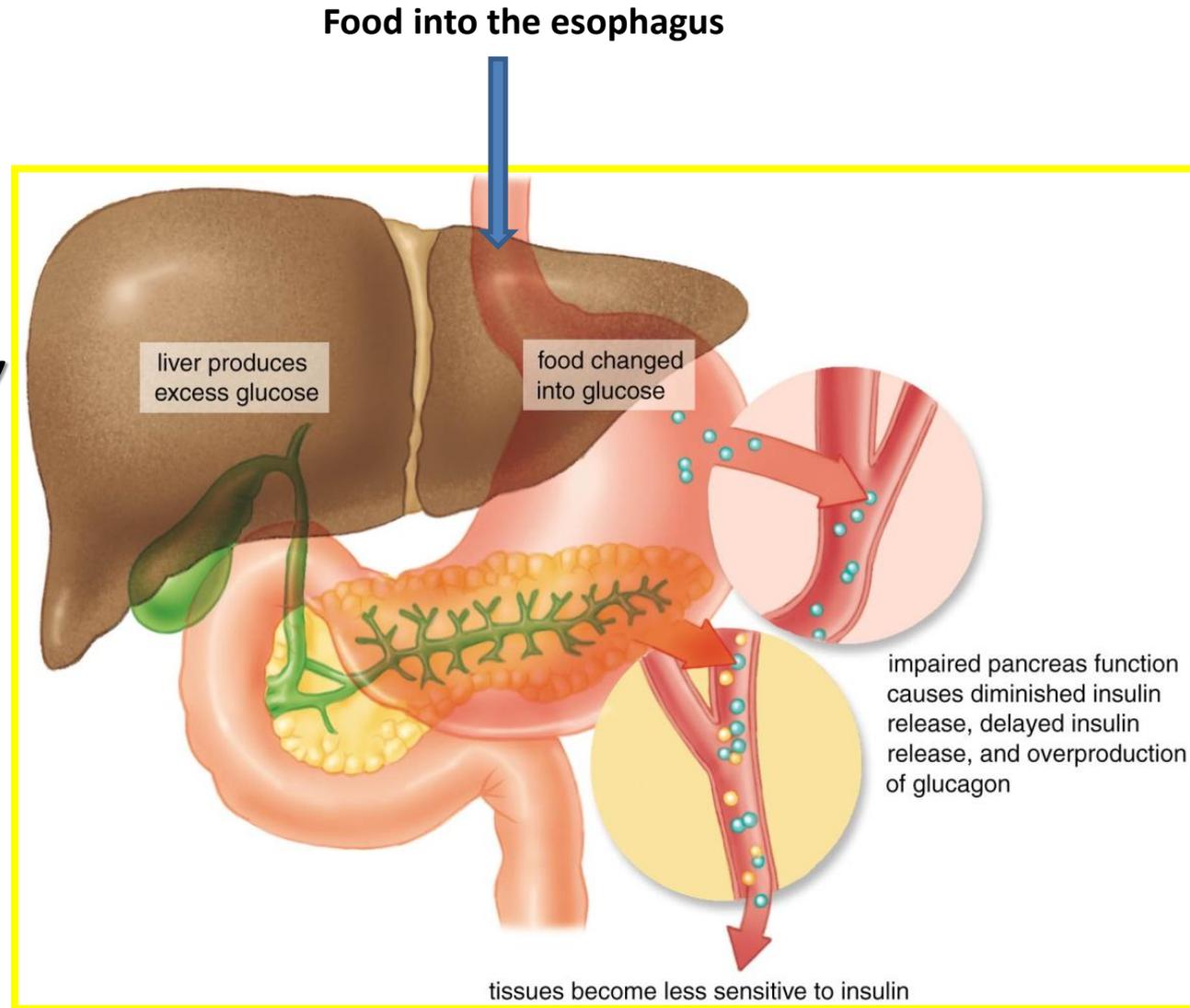
Type 1 Diabetes

The major cause is destruction of the beta cells of the pancreas by antibodies and therefore little or no insulin is produced.



Type 2 Diabetes

The major cause is ***insulin insensitivity*** (also called ***insulin resistance***) and ***impaired insulin production***.



Controversy

The classification of diabetes into type 1 and type 2 is likely oversimplified and perhaps confusing

There are probably many different types of diabetes.

Some examples are MODY(maturity onset diabetes of the young), Latent Autoimmune Diabetes of Adults (LADA) and multiple other types

It is probably more useful to divide the types of diabetes into autoimmune , or insulin resistant or combinations of both

Some authorities are already suggesting that the terms Type 1 and Type 2 be abandoned. **However, Type 1 and Type 2 diabetes are still the present way that diabetes is defined**

Diagnosis of Diabetes Mellitus

Fasting blood sugar greater than 126 milligrams per deciliter

Random blood sugar greater than 200 mg per deciliter

HbA1C (a blood test which reflects the average blood sugar over the past two months) greater than 6.5%

Symptoms of diabetes

- high blood levels of glucose
- blurry vision
- fatigue
- thirst
- painful urination
- frequent urination
- sores that do not heal
- nausea
- vomiting
- weight loss
- Hunger
- **In some cases...there are no symptoms at all!!
- **Diabetes type 1 and type 2 symptoms are closely similar, although, type 1 is often worse in severity



Microvascular and Macrovascular Complications of Diabetes

Retinopathy

Leading cause of blindness in adults.

Accounts for ~ 24,000 cases of blindness every year.

Nephropathy

Leading cause of end-stage renal disease (ESRD) in the United States.

Accounts for ~ 28,000 cases of ESRD every year.

Diabetes accounts for 1 of 3 patients with ESRD in the United States.

Myocardial Infarction and Stroke

Increased 2 to 4 fold.

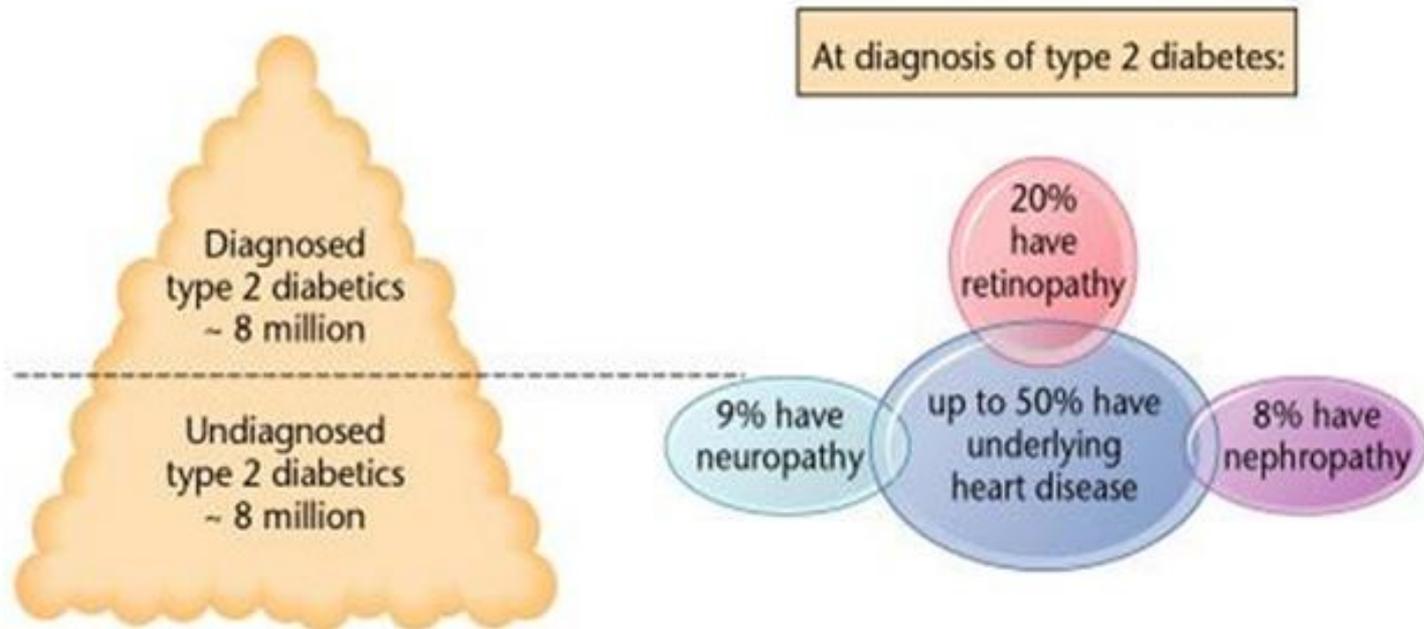
Accounts for 60% to 70% of all diabetes-related deaths.

Peripheral Vascular Disease

Leading cause of nontraumatic amputations.

Accounts for ~ 67,000 limbs lost per year.

Three year survival is ~ 50%.



This discouraging slide demonstrates that at the time of diagnosis of diabetes, complications of diabetes are already present

Timeline of the Modern History of Diabetes

1910

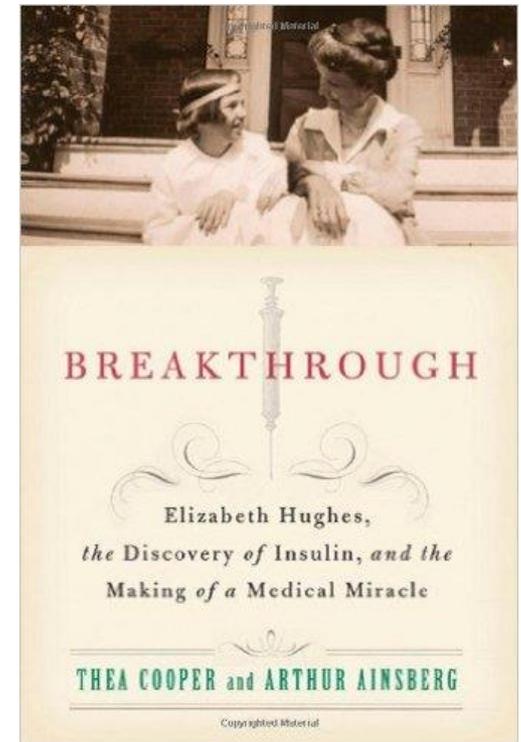
An English physiologist studying the pancreas, discovered a substance that would normally be produced in non-diabetics: **insulin**. The name comes from the Latin insula, meaning island, referencing the insulin-producing islets of Langerhans in the pancreas

Breakthrough

It was 1919 and Elizabeth Hughes, the eleven-year-old daughter of America's most-distinguished jurist and politician, Charles Evans Hughes, was diagnosed with juvenile diabetes.

It was essentially a death sentence. The only accepted form of treatment – starvation – whittled her down to forty-five pounds skin and bones.

In a race against time and a ravaging disease, Elizabeth became one of the first diabetics to receive insulin injections



Book about Elizabeth Hughes and her struggles with diabetes before the discovery of insulin.

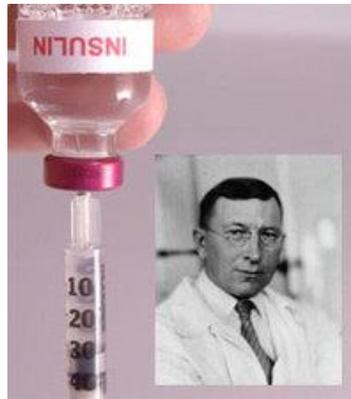
1921

Dr. Frederick Banting, a physician in Ontario, Canada hits upon the idea of obtaining insulin from the fetal pancreas.

He removes the pancreases from fetal calves and finds the extracts to be potent to treat patients with diabetes.

He first had the idea to use insulin to treat diabetes in 1920, and he and his colleagues began trying out his theory in animal experiments.

Banting and his team finally used insulin to successfully treat a diabetic patient in 1922 and were awarded the *Nobel Prize in Medicine in 1923.*



Dr. Frederick Banting

1923

Commercial production of insulin begins

1924

At a time when less than half of all babies born to mothers with diabetes survive, Priscilla White, MD, starts the Joslin Pregnancy Clinic.

NOTE THE 25 YEAR ABSENCE OF HIGHLIGHTS!!!

Research in diabetes virtually ceased after the succesful use of insulin

1949

The discovery that insulin works like a key, transporting glucose into cells.
(Much of this research was done at Vanderbilt in the lab of Dr. Charles Rollo Park)

1955

Sulfonylureas, oral medications that stimulate the pancreas to release more insulin, are available

1959

A method was developed for measuring insulin in the blood. It was found that some people with diabetes still make their own insulin, and they identify “insulin-dependent” (type 1) and “non-insulin-dependent” (type 2) diabetes.

1966

The first successful pancreas transplant is performed at the University of Minnesota Hospital.

1970

The first meter to measure glucose in the blood using fingerstick blood introduced

1972

The relationship between blood vessel disease and elevated blood sugar is reported.

1976

The first infusion pump using insulin was invented.

1977

Boston researchers develop a test to measure glycosylated hemoglobin (A1C). **A1C testing becomes the gold standard for measuring long-term diabetes control.**

1987

An autoantibody originally discovered in 1982 is found to be predictive of type 1 diabetes.

Researchers determine that tight control of glucose levels during pregnancy is important for the health of the baby, and continue to study how diabetes increases the risk for birth defects.

1993

The Diabetes Control and Complications Trial (DCCT), *which was conceived of and administered here at Vanderbilt by Dr. Oscar Crofford*, showed that keeping blood glucose levels as close to normal as possible slows the onset and progression of eye, kidney, and nerve diseases caused by diabetes. In fact, it demonstrated that any sustained lowering of blood glucose helps, even if the person has a history of poor control.

1994

It was shown that cholesterol lowering with statins markedly reduced the risk of myocardial infarction, stroke or death. The effect was greatest in individuals with diabetes.

1995

The drug metformin, now the most widely used drug for Type 2 diabetes, becomes available in the U.S.

1997

The terms “insulin-dependent diabetes” (IDDM) and “non-insulin-dependent diabetes” (NIDDM) had long been used to describe different groups of diabetes patients.

Type 1 diabetes and type 2 diabetes became the accepted terms to define diabetes by cause rather than treatment.

Fasting glucose level for diagnosing diabetes is lowered from 140 mg/dl to 126 mg/dl.

1998

The United Kingdom Prospective Diabetes Study (UKPDS) shows that people with type 2 diabetes who practice tight control of blood sugar levels and blood pressure levels reduce their risk of complications, similar to the results of the DCCT in people with type 1 diabetes.

Together these two studies transform the nature of diabetes care around the world.

2008

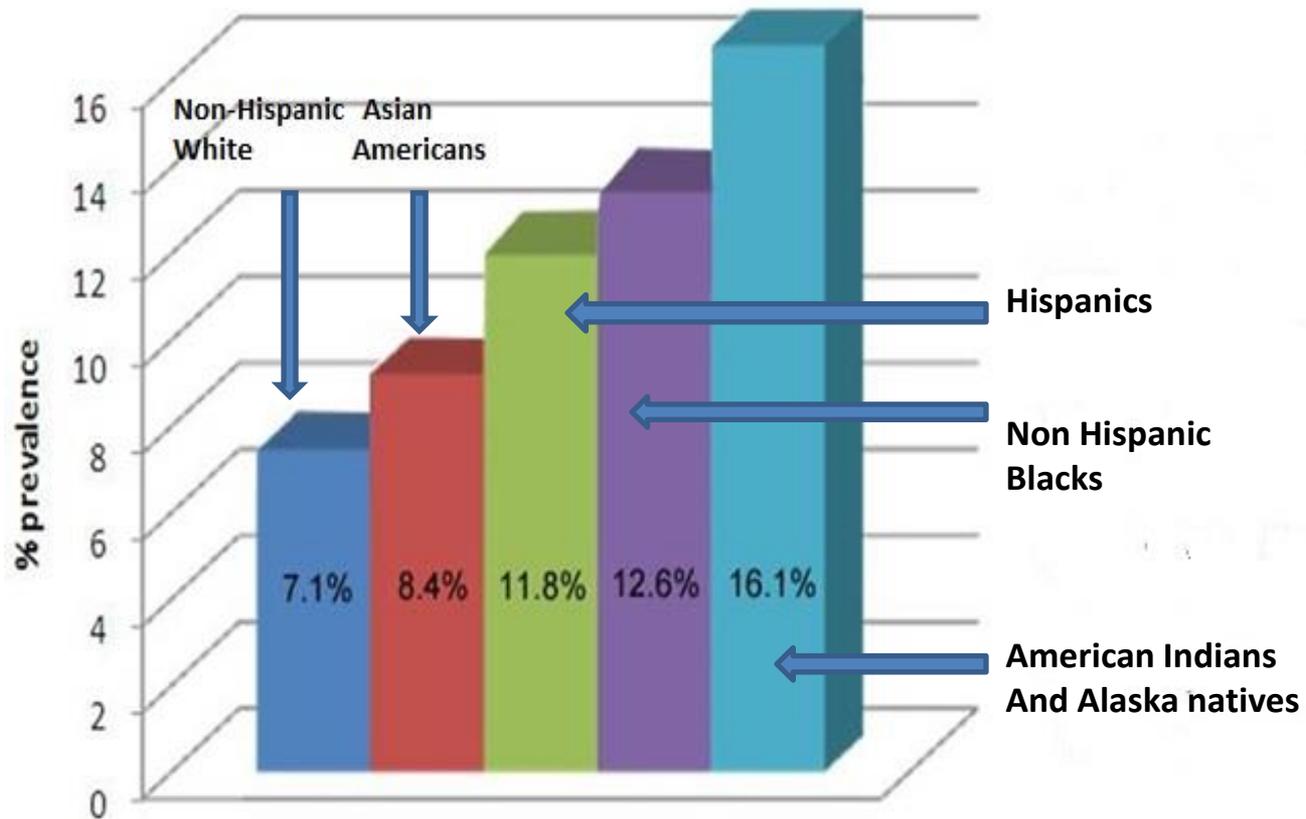
Three studies fail to show a benefit of intensive glycemic control on cardiovascular outcomes in people with type 2 diabetes who are at high cardiovascular risk.

2016

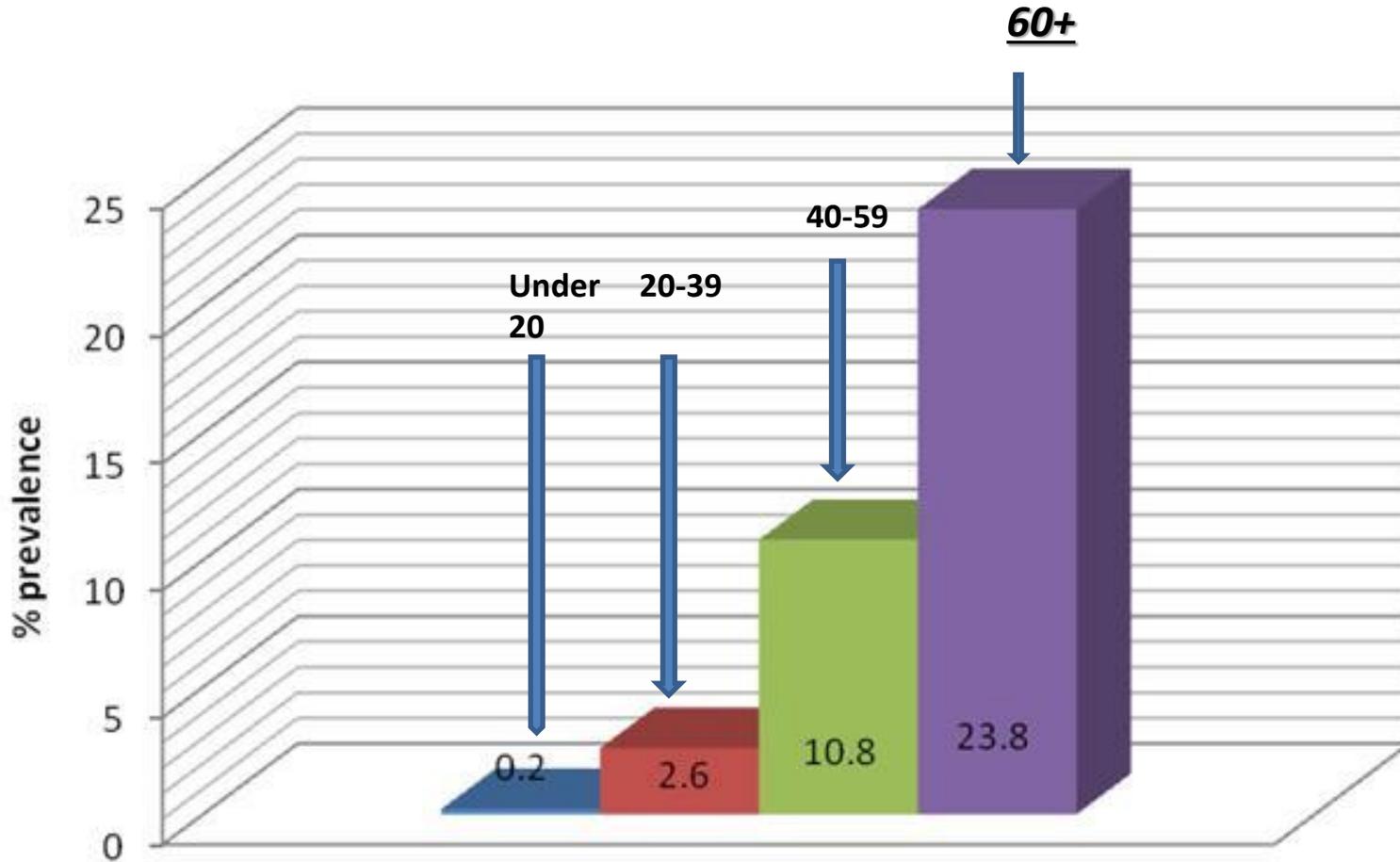
FDA approves 1st ***“Artificial Pancreas”***

Epidemiology and Financial Burden of diabetes

Prevalence of diabetes by Race/Ethnicity



Prevalence of Diabetes by Age



Probably 25% of this audience has diabetes now

Another 25% will have diabetes in 5 years

Tennessee Diabetes Statistics, Facts, and Death Rates

According to the American Diabetes Association, approximately 800,000 people in Tennessee or **14.9% of the population have diabetes, ranking it 6th highest in the nation.**

Of these an estimated **160,000 have diabetes but don't know it** which greatly increases their health risk.

Every year an estimated 36,000 people in Tennessee are diagnosed with diabetes

In addition, 1.7 million people in Tennessee (**35.8% of the adult population**) have **prediabetes with blood glucose levels higher than normal but not yet high enough to be diagnosed with diabetes**

30.2 out of every adult 100,000 deaths in Tennessee are due to diabetes, ranking Tennessee **10th highest in the nation for diabetes-related deaths.**

Source: [Tennessee State Diabetes Death Statistics.](#); [Tennessee State Health Facts.](#)

Diabetes is a costly disease. 1 in 7 health care dollars is spent on diabetes care in the United States.

Diabetes accounts for 27% of this country's entire Medicare budget.

Cost per patient per year

● Non-diabetic ● Diabetic

Hospital/nursing homes (Part A)



Medical/outpatient (Part B)



Prescription drugs (Part D)



Total



What's New in Diabetes

Can Type 1 Diabetes be prevented?

Not Yet

What is Type 1 Diabetes TrialNet?

Type 1 Diabetes TrialNet (TrialNet) is an international network of researchers who are exploring ways to prevent, delay and reverse the progression of type 1 diabetes

Can Type 2 Diabetes be prevented?

Yes, sometimes !

The Diabetes Prevention Program (DPP) was a major multicenter clinical research study aimed at discovering whether weight loss through dietary changes and increased physical activity versus treatment with the oral diabetes drug metformin could prevent or delay the onset of type 2 diabetes in study participant over a 5 year period

The DPP found that participants who lost a modest amount of weight through dietary change and increased physical activity sharply reduced their risk of developing diabetes by 58 percent during the study.

Metformin also reduced their risk of developing diabetes, but not as much as those in the lifestyle intervention group (approximately 30%)

What's new in diabetes

“Artificial Pancreas”

Insulin infusion pumps which infuse insulin under the skin have been available for about 25 years.

Patients using pumps had to check fingerstick blood sugars frequently to determine the rate of the infusion. This was called an open-loop system because the patient had to calculate the dose of insulin to be given.

Indwelling glucose measuring devices became available about 15 years ago. They were of limited usefulness but the accuracy has improved considerably.

The US Food and Drug Administration (FDA) has approved Medtronic's MiniMed 670G hybrid closed-loop insulin delivery system, the first-ever device that automatically monitors blood glucose and administers appropriate basal insulin doses , without the patients assistance, for patients aged 14 years and older with type 1 diabetes.

Because the device responds to both low and high blood glucose levels it is being called the first-ever "artificial pancreas."

THIS IS A MAJOR EVENT AND WILL CHANGE THE WAY TYPE 1 DIABETES WILL BE TREATED

The most exciting medical news or event in 2016 according to Medscape's members, a popular physicians forum, was FDA approval of the first "artificial pancreas" for type 1 diabetes, at nearly 31%.

A close second, at nearly 28%, was Donald Trump winning the presidency and the potential implications for healthcare policy.

Third was the cancer moonshot initiative (23%),

Last was the first device approved to treat insomnia (3%).

What's new in diabetes

Pancreas and Islet cell transplants

Pancreas Transplants

Many patients with type 1 diabetes have experienced positive results from pancreas transplants

A transplant of the pancreas is usually reserved for those with serious complications and *are most often done when a patient also receives a new kidney because of kidney failure caused by diabetes.*

The downsides are:

1. Waiting list for donors is *long* and *cost* is a major issue
2. The body treats the new pancreas as foreign and the immune system attacks the transplanted pancreas.
3. Transplant patients must take immunosuppressant drugs to prevent rejection of the new pancreas.
4. Drugs that suppress the immune system can lower resistance to other diseases, such as cancer, and infections.

Islet Cell Transplantation

Islets are clusters of cells in the pancreas that make insulin

Only 1-2% of the pancreas is made up of islet cells.

In pancreatic islet transplantation, cells are taken from a donor pancreas and transferred into another person. Once implanted, the new islets begin to make and release insulin

For an average-size person a typical transplant requires about 1 million islets, *equal to two donor organs.*

Because the islets are extremely fragile, transplantation occurs immediately after they are removed.

The transplant itself is easy and takes less than an hour to complete

A small catheter tube is placed through the upper abdomen.

The islets are then injected through the catheter into the liver

The downsides are:

1. Immunosuppressive or anti-rejection drugs are needed to keep the transplanted islets functioning
2. Unfortunately, the islet cells do not survive very long and therefore islet cell transplantation is still experimental
3. A great deal of research is ongoing in this field and it is promising
4. ***Eventually, islet cell transplants will replace pancreas transplants***

A New Approach to Islet Cell transplant Under Investigation

Previously, scientists have attempted to artificially cultivate islet cells from patients' stem cells

There has been difficulty manufacturing the cells at the scale necessary for clinical use, and the cells are naturally prone to dying off once introduced into the body

Human kidney cells growing in tissue culture were engineered to perform the function normally carried out by the pancreas including manufacturing insulin.

Two genes were introduced into the cells – one to make them sensitive to glucose levels and a second to instruct the cell to pump out insulin when glucose levels exceeded a threshold.

Tested in mice, this therapy involves a capsule of these genetically engineered kidney cells, implanted under the skin that release insulin as required

Scientists said they hope to obtain a clinical trial license to test the technology in patients within two years.

If confirmed as safe and effective in humans, diabetes patients could be given an implant that would need to be replaced three times a year

What's new in diabetes

Oral Insulin

The development of an oral form of insulin has been a work in progress for many years.

Many ideas are in the works from sprays to pills. Inhalable insulin has been available for many years but has limited use

The difficulty with pills is that insulin, being a protein, gets easily destroyed by digestive juices in the stomach and small intestines.

Finding a coating for the pill that would protect it once it reached the stomach was the initial problem.

However, there is now an oral insulin pill that is entering Phase III clinical trials.

When insulin is available that can be taken by mouth, diabetes care will enter a whole new dimension

What's new in diabetes

Treatment Options In Obesity

Surgical Treatment Option

Gastric bypass has been around for many years primarily for the treatment of morbid obesity.

It was fraught with many complications and was of only limited use

However, this operation has improved considerably along with newer procedures such as gastric banding which is actually done through a laparoscope .

These new procedures are much safer.

When these procedures are done on obese patients with type 2 diabetes, amazingly the ***blood sugars quickly fall within a matter of a few days long before weight loss occurs***

Why this occurs is unclear

There are obviously hormones in the gastrointestinal tract which affect blood sugar.

Medical Treatment Option

Advances are being made in the medical treatment of obesity.

Many new drugs are coming on the market rapidly

So far the expense, efficacy, and safety have led to their limited use.

However, the future of the treatment for obesity will be safe, inexpensive medication which will greatly help to attack the epidemic of diabetes and obesity.

What's new in diabetes

New Medications for Diabetes

There are a multitude of new medications on the market for the treatment of type 2 diabetes

The FDA has recently approved a medication presently on the market *which decreases mortality* in patients with diabetes and preexisting heart disease

Another medication recently presented to the FDA has a unique delivery system which is implanted under the skin and lasts for six months before it needs replacing

Unfortunately, the expense of medications has driven the cost of treatment out of sight

There are many more drugs in the pipeline.

These medications will shed more light on the pathophysiology of type 2 diabetes and will add greatly to our armamentarium

In summary, the future for patients with diabetes is exciting.

10 years from now, the diagnosis and treatment for diabetes will be much different than today.

However unless preventive and “curative“ measures are successful, diabetes will remain a chronic disease and patients will have to deal with it long term

A copy of the slides is available at the following link:

<https://www.dropbox.com/s/tia7obfny73mgsz/Intellectual%20sampler%20.pptx?dl=0>