Homeostasis

Regulation of the Internal Milieu

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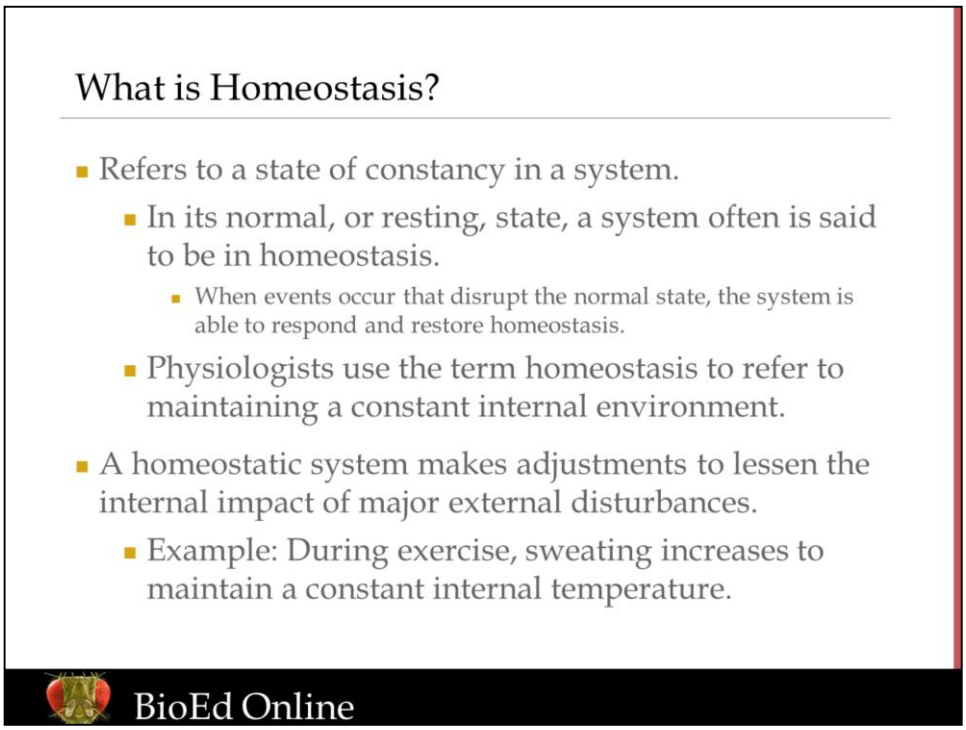

What is Homeostasis?

Homeostasis is a term that refers to constancy in a system. To physiologists, homeostasis means "maintaining a constant internal environment." The internal environment usually is thought of as the extra-cellular fluid (ECF) that constantly bathes the cells, providing nutrients and carrying away wastes. If a system is in homeostasis, it is in its normal, or resting, state. If disturbances disrupt the normal state, the system will act to restore the normal state. For example, a person who is standing still has a normal resting respiratory rate. If that person runs as fast as he/she can for 30 seconds, his/her respiratory rate will increase to meet the body's demand for oxygen. During the run, the body uses more oxygen than it does when it is standing still. To maintain homeostasis, the respiratory rate increases to meet the increased demand. Furthermore, when the person returns to a resting state, the respiratory rate eventually will return to a normal rate because of the decreased demand for oxygen.

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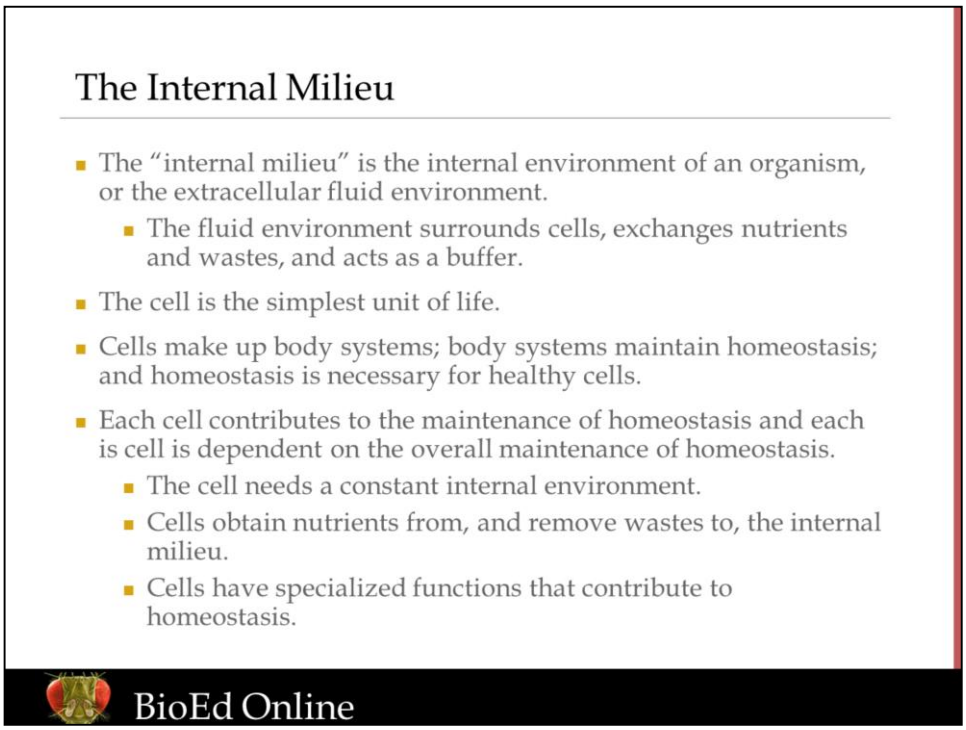

The Internal Milieu

The cell is the simplest unit of life. Unicellular organisms typically perform all of life's functions. The cells of a multicellular organism, however, depend on other cells for their health, and also are responsible for the health and proper functioning of other cells and the organism as a whole. To survive, the cell needs a relatively stable internal milieu. Cells within an organism make up body systems. In turn, body systems respond to some external changes in ways that lessen the impact of those changes on the body, and thus, help to maintain the stable internal environment ("internal milieu") needed by cells.

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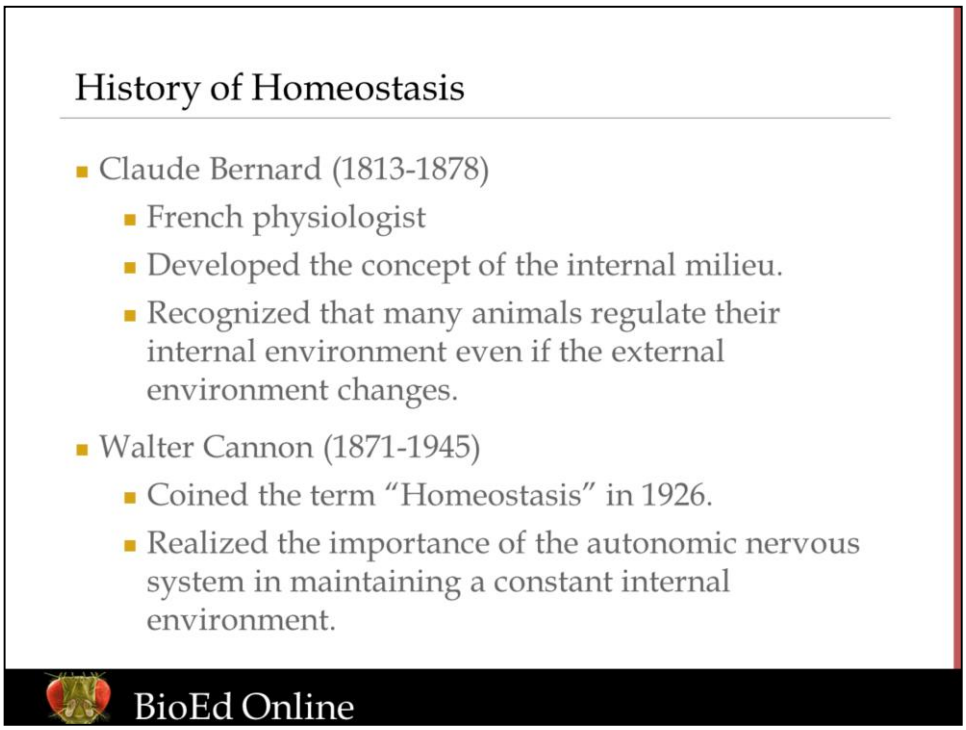

History of Homeostasis

Claude Bernard was a French physiologist who usually is credited with developing the concept of the "internal milieu" (internal environment). He astutely observed that animals can regulate their internal environments–and maintain a favorable state–even if the external environment changes.

Walter Cannon was a prominent American scientist who coined the term, "homeostasis," when referring to a constant internal environment. He wrote prolifically on the subject and was a pioneer in the study of the autonomic nervous system's role in maintaining homeostasis.

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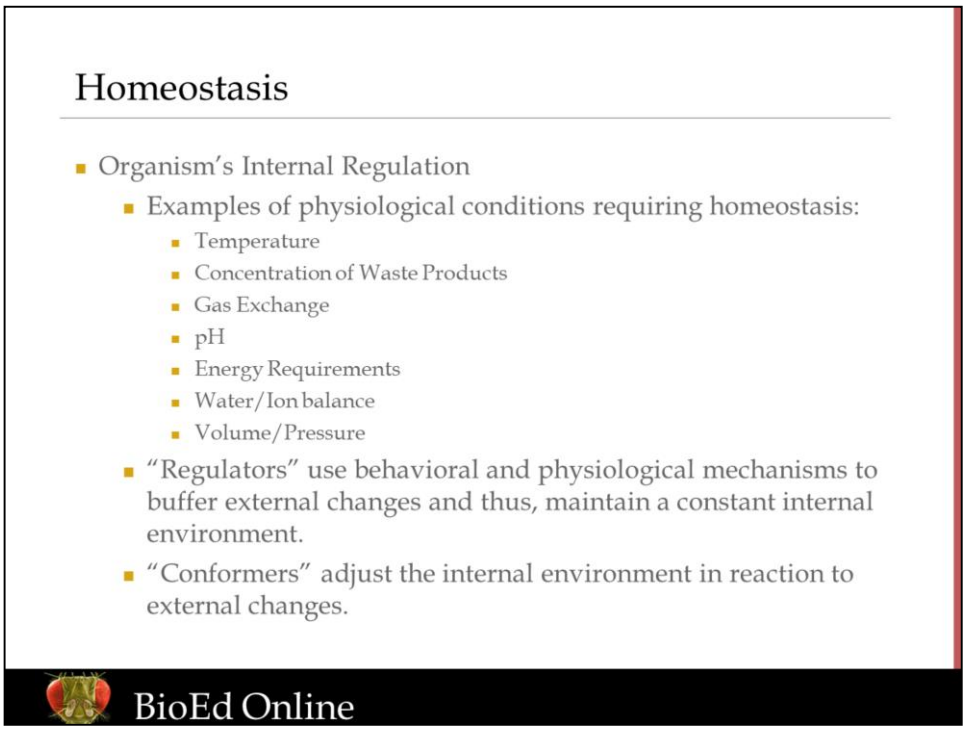

Homeostasis

In biology, homeostasis can describe an individual organism's internal regulation as well as the regulation of an entire population of organisms. This presentation focuses on the individual. If an individual organism is unable to maintain homeostasis (i.e., regulate its body temperature, pH, water balance, ion balance, etc.), it will suffer dire consequences. And how do organisms maintain homeostasis? Some organisms, called regulators, are able to buffer the impact of external changes and thus, maintain the internal environment by using various behavioral and physiological mechanisms. Other organisms, called conformers, live in very stable environments and have not evolved such maintenance mechanisms. Since their environments are very stable, the "cost" of such mechanisms outweighs the benefits gained from them. These organisms' internal environment can change with the external environment because in these cases the external environment changes very little. A microorganism living in extremely salty conditions is a "conformer." Humans, on the other hand, are "regulators."

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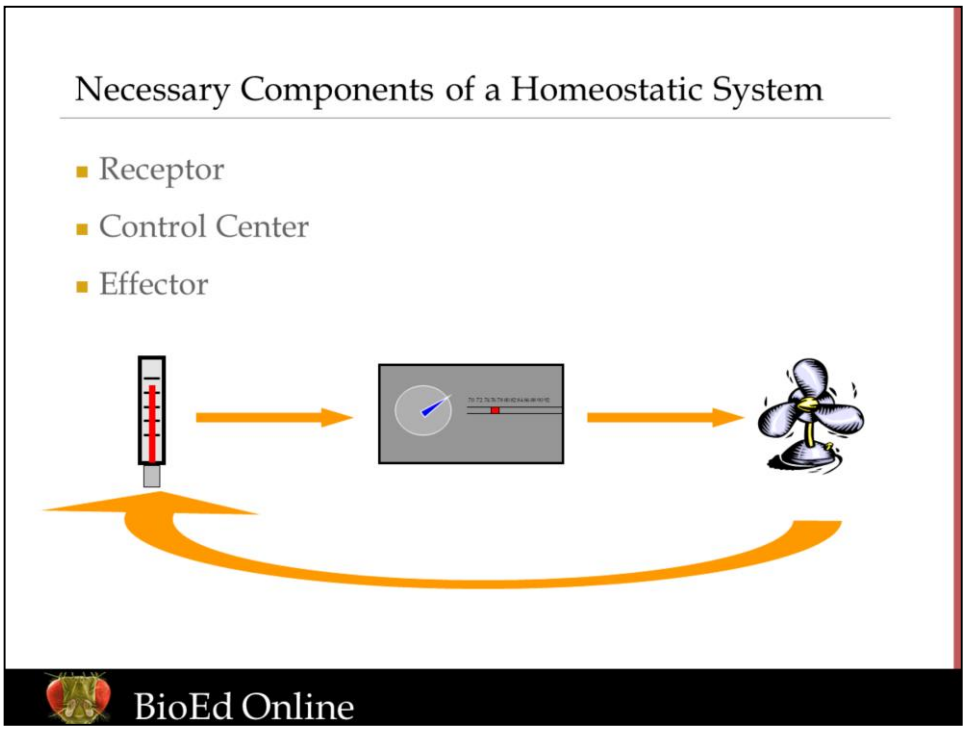

Components of a Homeostatic System

To maintain homeostasis, a system must have three components: 1) a receptor, 2) a control center, and 3) an effector. All of these components do specific jobs that allow an organism to regulate its internal environment. A receptor detects external changes that could influence the internal environment. It then reports these changes to the control center, which, in turn, will activate an effector, whose function is to restore homeostasis. In the diagram above, the thermometer represents the receptor for this homeostatic system. It communicates with the thermostat (the control center) when there is a change in the external environment. The thermostat responds by directing the fan (the effector) to turn off or on. For example, if the thermometer informs the thermostat of a sudden increase in temperature, the thermostat will direct the fan to turn on to cool the area back to a comfortable temperature.

The central nervous system and the endocrine system are the major control systems in the body. Each is able to respond to signals from receptors and activate effectors accordingly.

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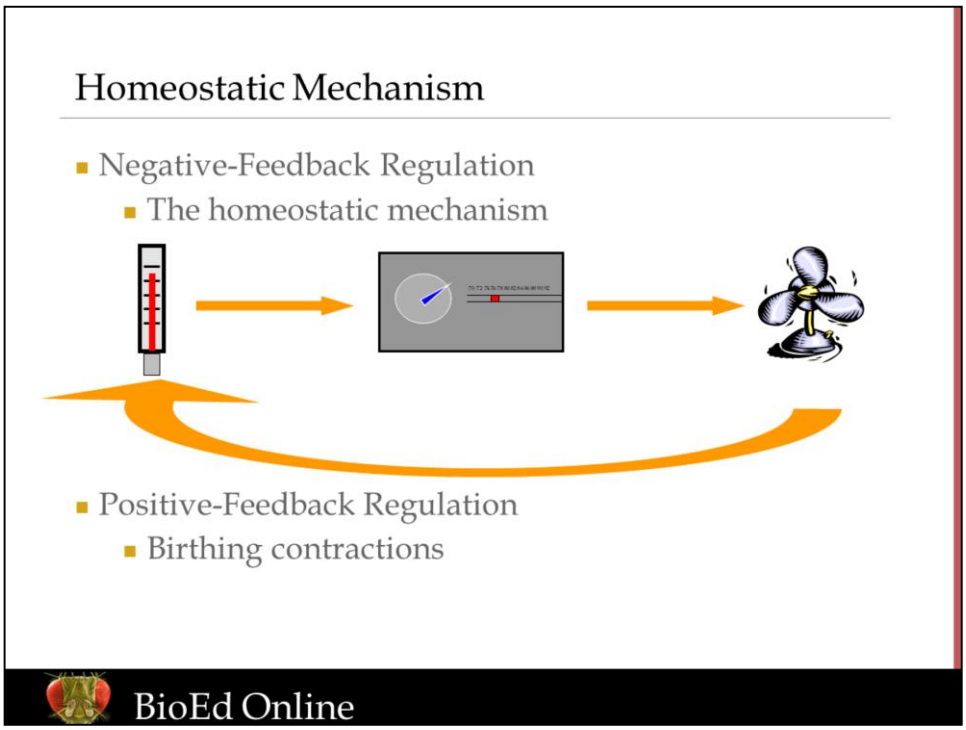

Homeostatic Mechanism

The mechanism known as negative-feedback regulation maintains homeostasis. The "receptor, control center, effector" structure of a homeostatic system (described in the previous slide) enables negative-feedback regulation to occur. When a large external change is detected by the receptor, a signal is sent to, and is interpreted by the control center, resulting in a response by the effector to minimize the internal impact of the large external change. This is negative-feedback regulation. The original external change is counteracted internally so that the internal change is small or nonexistent.

Positive-feedback regulation also is seen in biological systems, but it is not utilized for maintaining homeostasis. Rather, positive-feedback is used to augment a change within an organism. For example, during birth, the uterus contracts to expel the infant. Positive-feedback causes these contractions to continue until the birth is complete. So, whereas negative-feedback helps homeostatic systems to remain fairly constant by responding to changes in the external environment, positive-feedback promotes the change.

References

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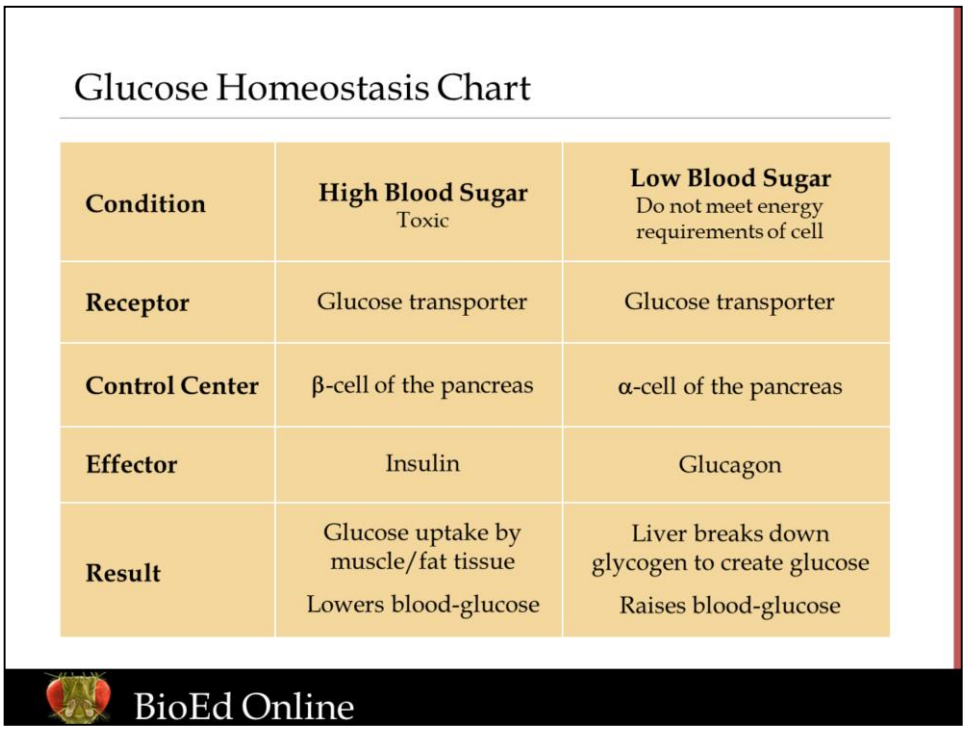

Glucose Homeostasis Chart

Glucose is used by many organisms as fuel, but it is vital that glucose levels be tightly regulated. Too little glucose will lead to starvation, while too much is toxic. Glucose homeostasis is accomplished through highly complex mechanisms involving many different molecules, cell types, and organs.

Briefly, when glucose enters the bloodstream (after the digestion of food), it is detected by specialized cells in the pancreas, called β-cells. These cells respond to the rising blood-glucose concentration by releasing the enzyme, insulin. Insulin then signals to other tissues in the body (i.e., muscle cells and adipose tissue) to take in glucose to be used as energy (in muscle cells) or stored for later use (in adipose tissue). The result is a lowering of blood-glucose concentration to non-toxic levels.

In times of low glucose intake (between meals or in cases of starvation) the α-cells of the pancreas release the enzyme, glucagon. This enzyme directs the liver to break down stored glycogen into glucose and release this glucose into the bloodstream, thereby raising blood-glucose concentration to a desired level. The glucose transporters expressed on the β- and α-cells that bind glucose are the receptors of this homeostatic system. The β- and α-cells, themselves, are the control centers. They process information from the receptors and respond to it in a way that will maintain a constant internal environment. Insulin and glucagon are the effectors. This system is complex; the β- and α-cells working continuously to achieve the optimal, homeostatic blood-glucose concentration.

References

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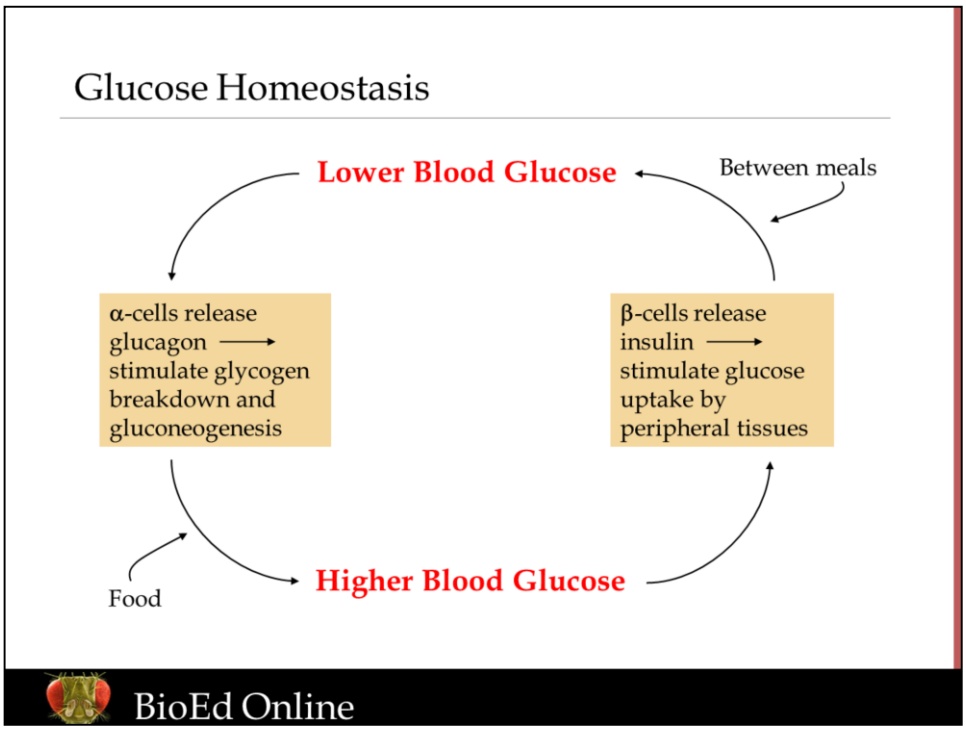

Glucose Homeostasis

Here is a diagram of glucose homeostasis. When we eat food, our blood glucose concentration rises, which stimulates insulin secretion from β-cells and eventual glucose absorption by peripheral tissues. In between meals or in times of starvation, we are not taking in glucose and, therefore, experience a drop in blood glucose. During these times, the α-cells release glucagon, which stimulates the liver to make glucose by glycogenolysis and gluconeogenesis, and thereby raise blood glucose to normal levels.

References

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Disruption of Homeostasis

There are numerous ways to disrupt homeostasis, and the results of this disruption can vary in severity. Failure to achieve or restore homeostasis can result in death, which can be considered the ultimate disruption of homeostasis.

Injuries can have severe homeostatic consequences. A punctured lung, for example, will disrupt the flow of oxygen to the body. Cells in the brain cannot be deprived of oxygen for extended periods of time without dire consequences.

Illness also will cause a temporary disruption of homeostasis. Fever, a common symptom of a cold or flu, is a disruption of the body's constant internal temperature. It usually is a sign that our body is fighting an infection of some type and, therefore, might be considered a good sign. After the illness subsides, the fever breaks and the normal, constant body temperature is re-achieved. However, an unchecked fever can damage neurons and organs, or even result in death..

Some disruptions in homeostasis are genetic. For example, a disease such as diabetes, to which some people have a genetic predisposition, can disrupt homeostasis. In addition, lifestyle factors such as obesity, lack of exercise, and a fatty diet—which also can disrupt homeostasis—have been shown to enhance one's chances of becoming diabetic. Not surprisingly, an individual with poor health habits is more likely to have problems maintaining homeostasis than a person with good health habits.

References

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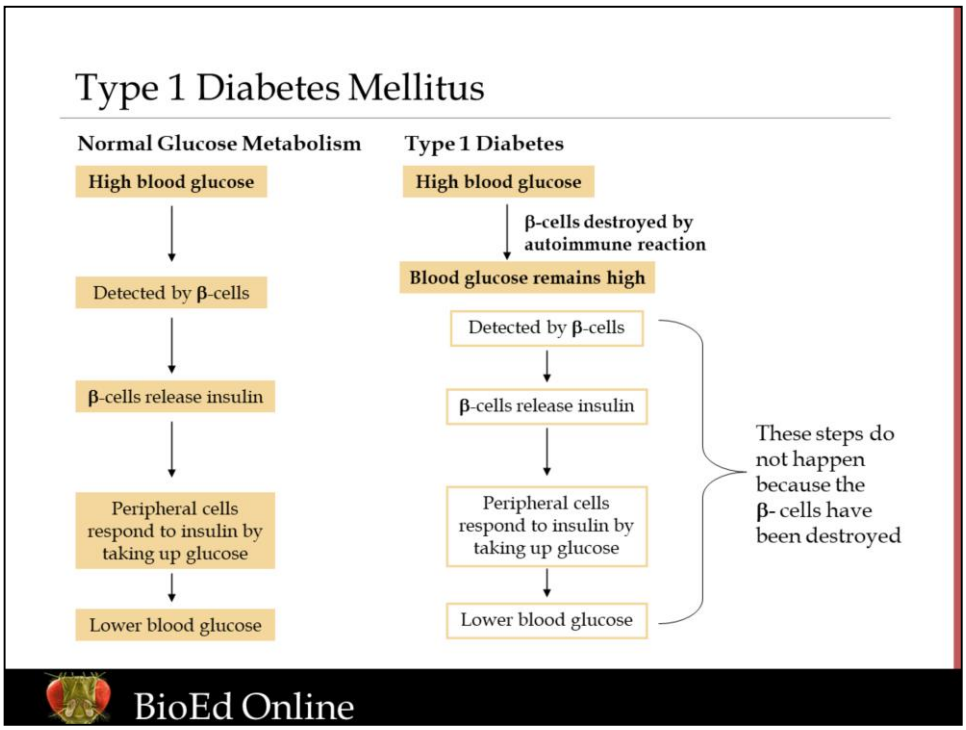

Type 1 Diabetes Mellitus

This diagram shows where in the glucose metabolic pathway Type 1 diabetics differ from healthy individuals.

Type 1 diabetes is an autoimmune disorder, meaning the body's immune system is not functioning properly and attacks the body itself. In Type 1 diabetes, the antibodies produced by the immune system bind to the β-cells, which then are destroyed by specialized immune cells. Because the β-cells are destroyed, no insulin is produced, and therefore, the peripheral tissues (muscle and fat) do not receive a signal that allows for glucose uptake. Ultimately, this condition causes glucose levels in the bloodstream to remain high. Individuals with Type 1 DM are dependent on exogenous (produced outside the body) sources of insulin.

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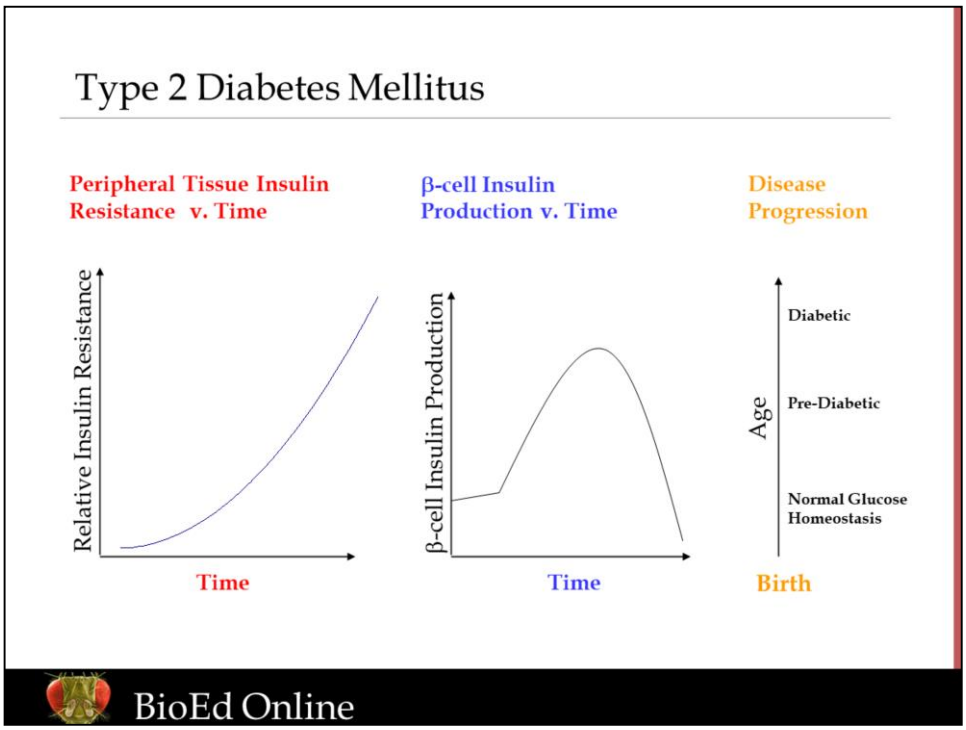

Type 2 Diabetes Mellitus

Type 2 diabetes is most common in older individuals, because it takes time for this disease to develop (for this reason, we say it has an insidious onset). The classic model of Type 2 diabetes shows us that over time, the peripheral tissues become insulin resistant. In other words, the body is no longer responding to the insulin signal. Therefore, after glucose ingestion, even in the presence of insulin, the blood glucose concentration remains too high. Furthermore, because the liver is also resistant to insulin, glycogenolysis and gluconeogenesis are not terminated. Thus, the body has a high blood glucose concentration due to the inability of the peripheral tissues to take in glucose AND because the liver is synthesizing glucose.

As seen in the simplified second graph, β-cell Insulin Production v. Time, we see that the β-cell compensates for resistance by increasing the production of insulin. The β-cell is able to produce enough insulin to overcome the resistance and maintain normal blood glucose levels. However, eventually, the β-cell becomes exhausted from this work over-load. At that point, the peripheral tissues are resistant to insulin and the body is not producing enough insulin for a normal individual.

This process does not happen overnight. As the graph illustrates, an individual may have normal glucose homeostasis for the majority of his/her life. However, as insulin resistance progresses and β-cell function is diminished, a person will become "pre-diabetic." At this stage of the disease, a person may not know that he/she is affected. Nonetheless, his or her body is gradually losing its ability to control blood glucose levels. As the disease progresses, full-blown diabetes ensues and treatment options become more and more limited.

Although insulin resistance usually develops over years, there is an alarming increase in the incidence of Type 2 diabetes among children. Many believe this trend is a result of less active children who may not be exercising sufficiently or eating healthy foods.

Diabetes is a complex disease, and as you have learned from the previous slides, there is more

than one way to become diabetic. The end result is the same for both Type 1 and Type 2 diabetes, if left untreated: loss of glucose homeostasis, which can be fatal.

References

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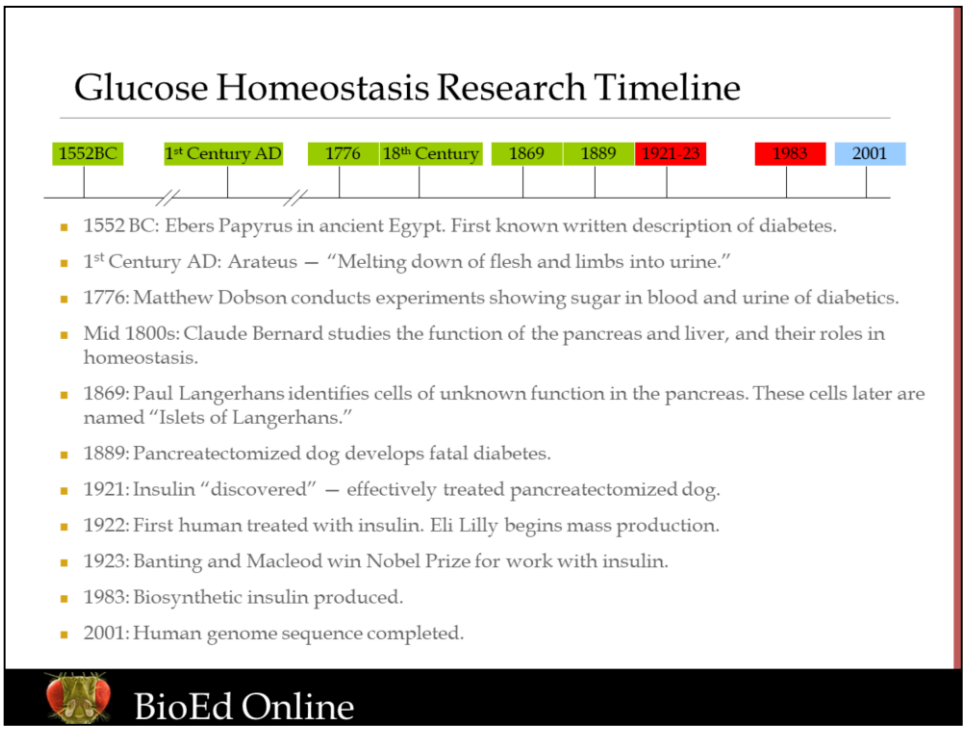

Glucose Homeostasis Research Timeline

George Ebers found the Ebers Papyrus in Egypt in 1872. The papyrus is the first known written description of diabetes, and while it is dated to 1552 BC, it contains references contained that date to earlier than 3000 BC. In the 1st Century AD, Arateus famously explained diabetes as the "melting down of flesh and limbs into urine." Early physicians understood that polyuria (frequent urination) was a symptom of diabetes, but it was not until 1776 that Matthew Dobson was able to show that the sweet taste of a diabetic's urine was attributed to glucose in the urine.

The "Experimental Period" of diabetes began in the mid-19th Century. The efforts of Claude Bernard, who studied the workings of the liver and pancreas in digestion; the identification by Paul Langerhans of cells of unknown function residing within the pancreas (later called "Islets of Langerhans"); and the pancreatectomy of a dog that resulted in fatal diabetes greatly expanded the understanding of diabetes and glucose homeostasis.

Research continued, and in 1921, insulin was used successfully to treat a pancreatectomized dog. The next year, a 14-year-old diabetic boy also was treated successfully with insulin. This resulted in the Nobel Prize for Medicine for Frederick G. Banting and John James Richard Macleod (both from the University of Toronto). Banting shared his monetary prize with his 22-year old research assistant, Charles Best. Macleod shared his winnings with a biochemist, James Collip. With the advent of molecular biology, research in diabetes led to new pharmaceutical approaches to treatment. In 1983, the first biosynthetic insulin became commercially available, increasing supply and making production relatively cheap, compared to harvesting insulin from pigs and cows. Then, in 2001, the initial draft of the Human genome sequence was completed. This detailed knowledge of man's genetic composition is leading to new discoveries, but with the complex nature of diabetes (multiple genes, environmental component), the disease still remains largely a mystery.

References

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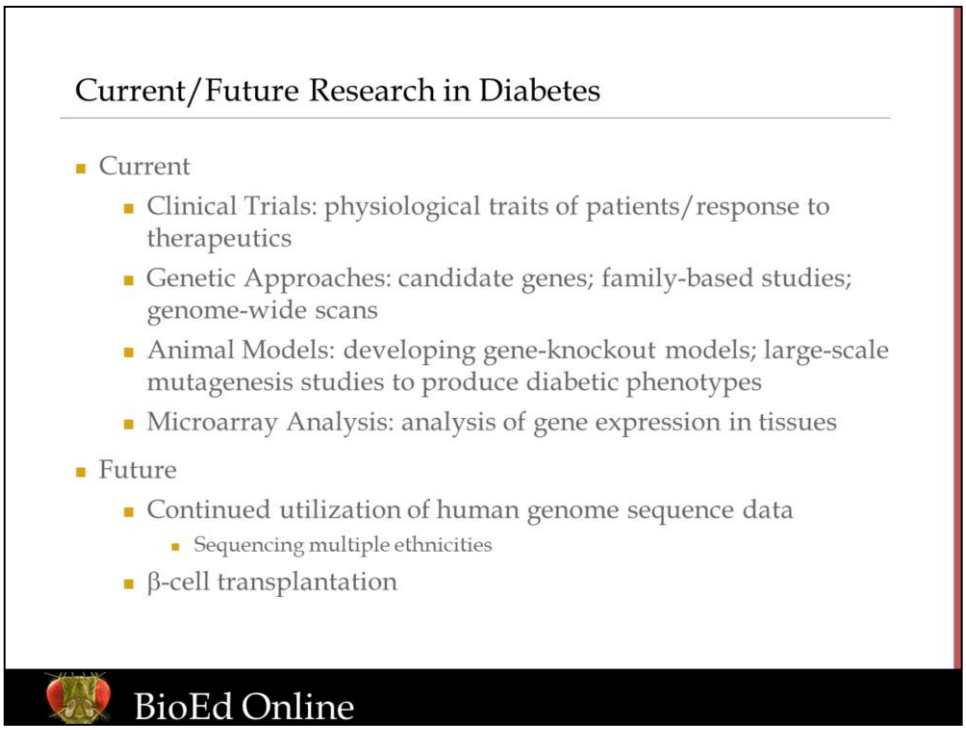

Current/Future Research in Diabetes

Currently, there are two major places in which researchers are studying diabetes and its treatment: the clinic and the laboratory. Clinical trials involve physicians treating patients, and then studying how patients respond to medicines and treatments. Typically, clinical trials involve many affected and unaffected individuals; they are time consuming. However, clinical trials also are a continuous source of new insights into metabolic disorders.

Laboratory scientists are utilizing many approaches to studying disease. Genetic approaches include, but are not limited to, studying candidate genes (genes in a particular pathway implicated in disease); family-based studies in which geneticists trace the inheritance of disease alleles; and genome-wide scans. Genome-wide scans are labor-intensive assays that study biomarkers across the entire human genome. The goal is to locate markers that associate only with disease or unaffected populations.

Animal models are used extensively in the study of disease. Mouse knock-outs (a particular gene of interest is missing) provide valuable insights into the functional properties of gene products (proteins). Large-scale mutagenesis strategies tend not to be directed, but if a particular phenotype of interest is generated, researchers can work back to the disease-causing genotype. Finally, microarrays can examine the expression of all genes in a given tissue in one experiment – thereby generating a tremendous amount of data. Genes that are expressed in healthy individuals but not in affected individuals (and vice versa) are of much interest.

With the generation of the human genome sequence, research into complex diseases is progressing rapidly and beginning a new phase of high-throughput, high-yield data generation. Use of these data to resequence known disease genes or plausible candidate genes is advancing research daily. Furthermore, as sequencing technologies become more ubiquitous, we are quickly approaching a time when DNA will be sequenced in a physician's office and the molecular diagnosis will allow more effective treatment. This is a goal of "personalized-medicine."

Finally, the clinic also is progressing, thanks to all the new technologies available. One technology generating much excitement in the field of diabetes research is β-cell transplantation. Infusion of healthy β-cells into severe diabetics has been shown recently to enhance the patient's ability to manage his/her disease drastically.

Although there has been much progress, much is left to learn. With all of the new technologies and increased emphasis on biological research, we still find ourselves in the midst of a diabetic epidemic that will affect an estimated 300 million people by the year 2025. Furthermore, there is an alarming increase in the number of diabetic children, which correlates to the increase number of obese children in the U.S. Technology and research will continue to advance and shed light on the genetic causes of disease. However, the diabetic epidemic will be reduced only if these advances are combined with healthy lifestyles.

References

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Conclusion

- "Homeostasis" is the ability of the body to maintain a constant internal environment by making small internal adjustments to compensate for large external disturbances.
- Injuries, illness, disease and death can disrupt homeostasis.
- Diabetes causes disruption of glucose homeostasis. It is only one example of the potentially severe problems caused by disrupting homeostasis.
- Science is actively pursuing a broader, more detailed understanding of homeostatic mechanisms and the consequences of their disruptions.

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