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The Challenge to Deliver Insulin

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by Chris Willems

Objective

The Challenge to Deliver Insulin curriculum unit is intended primarily for the high school biology and chemistry classroom. This unit includes background on chemistry and cellular functioning as it relates to diabetes. Main instructional topics include protein chemistry, transcription, translation, and insulin evolution. Classroom activities that investigate these fundamental chemical and cellular processes are included to bring the unit directly to the students' lab bench.

Protein synthesis is a complicated, abstract concept for students to master, and the model of a familiar disease should make the topic more relevant and engaging.

Genetic engineering and microbiology is a topic that is frequently misunderstood by students. In the case of insulin, inserting the human genetic code for insulin into *E. coli* bacteria allows pharmaceutical companies to manufacture insulin that is safe to use in people, as it is identical to the insulin that is found in their own bodies. Insulin production is an illustration of how modern medicine is a combination of scientific knowledge, careful experimentation, successful application, and practice that saves human lives.

Students do not readily accept that bacteria exist everywhere. There are more bacteria in the average human intestinal tract than there are humans on earth! While some bacteria are pathogenic, most are not. Bacteria play extremely important roles in modern medicine - both as a source for biomolecules such as insulin and as a nettlesome invader in tissue engineering and when introducing new devices to the human body.

Bacteria and other cell types have had their genomes successfully altered in the name of modern medicine in many other situations. For example, erythropoietin has been cloned to treat anemia, granulocyte-colony stimulating factor has been cloned to treat blood disorders, interferons have been cloned to act as anti-viral and anti-tumor agents, and nerve growth factor (NGF) has been cloned to promote nerve damage repair. (1)

Insulin is also an interesting molecule to consider with respect to the evolution of myriad different organisms. Sugars are a very convenient food source for most organisms, and the molecular relationship among different species' insulins is interesting to examine.

Rationale

Americans have constant access to food. This recent development is one that is having a disastrous effect on our health. Our ability to metabolize calories has not changed, and the result has been a skyrocketing rate of diabetes, obesity, and heart disease.

This unit is of particular relevance to New Haven, Connecticut students. New Haven is a city of 124,000 whose population lives with the same diseases commonly found in the poor, inner cities of today's United States. Obesity, diabetes, heart disease, asthma, HIV, and other diseases are present at a disproportionately higher rate in this population. Nationally, diabetes afflicts over 20 million people, or 7% of the U.S. population, and it kills 225,000 annually - a 22 percent increase since 1990. (2) The literature frequently uses the word "epidemic" to describe obesity and the concurrent spread of type 2 diabetes. (3)

Diabetes is the sixth leading cause of death in the United States. Diabetes increases the risk of stroke and heart attack. When compared to an individual of the same age without diabetes, the overall chance of dying doubles.

As with many diseases, diabetes seems to have a genetic "susceptibility" component.

African Americans are 1.8 times more likely than non-Hispanic white adults to have diabetes and Hispanics are 1.7 times as likely as non-Hispanic Whites to have diabetes. This is particularly disturbing when considering that over 85% of New Haven's students are at elevated risk of becoming diabetic: New Haven had a total student enrollment of 20,759 in the 2005/2006 school year. Of these students, African Americans represented 54.82%, or 11,380 students, and Hispanics represented 30.95%, or 6,425 students. (4)

Diabetes mellitus

Diabetes mellitus is a combination of two Greek words: diabaínein means "passing through," and is a reference to the excessive urination common to diabetics. Mellitus means "honey," in reference to the sweetness of the blood and urine of diabetics.

In diabetes, the lack of the protein hormone insulin leads to a build up of glucose (sugar) in the blood. This condition of excessive blood sugar is called hyperglycemia.

When this happens, patients may experience glycosuria; they release glucose dissolved in water in their urine. Patients urinate more frequently (polyuria) so more glucose can be removed. In addition to increased urination, symptoms of this condition are thirst and excessive drinking (polydypsia), due to the endocrine system's response to water lost. If the patient drinks more fluid, more sugar will be lost

For people with kidney (renal) failure, dialysis via ultrafiltration is the process, where waste product molecules (urea), undesired ions, and excess glucose can be removed from the bloodstream. Other proteins and blood cells remain in the blood stream, as they are too large to pass through the openings in the membrane. (5)

Kidneys are organs located near the middle of your back, and are about the size of your fist. Kidneys process about 200 quarts of blood per day and remove about two quarts of waste dissolved in water. In the specialized filtration system of the kidney (nephrons), waste passes from the bloodstream, through the nephron, and into the tubules that lead ultimately to the bladder.

Nearly half of the new renal failure cases in the United States are a result of diabetes.

Osmotic diuresis (excessive urination) is a result of too much sugar being filtered, and not being able to be reabsorbed by the tubules of the kidney. Diabetic nephropathy is the destruction of the nephrons of the kidney by excessive sugar in the blood.

The ideal blood sugar level is 80-120 mg/dl. Values above 200 mg/dl are dangerous, lead to polyuria and polydypsia, dehydration, and indicate a situation that requires medical attention.

Diabetics also frequently lose weight. As they are not properly obtaining energy from the food they consume, the body uses other sources of energy in the body, such as stored proteins and lipids.

Due to the stresses on the human body outlined above, diabetes is a disease that causes weakness, fatigue, and decreased alertness. Additionally, not having insulin leads to breakdown of entire endocrine system. It is striking to realize that the loss of one compound can cause a disruption to a vital system.

The two major types of Diabetes

"Type 1" was formerly called "juvenile onset" or "insulin-dependent" diabetes. Type 1, the less common form of diabetes, affects about 5% to 10% of all diabetics. In this form of diabetes, the immune system attacks and destroys the pancreatic beta cells that produce insulin. It usually develops in patients by age 15.

"Type 2" diabetes, also called "non-insulin dependent" or "adult onset," is now being seen much more frequently in children. It is the most common type of diabetes (90% to 95% of U.S. cases) and is a result of the body not properly using insulin produced by islet cells. Blood sugar rises to dangerous levels as the cells do not store glucose as glycogen, and glucose continues to enter the bloodstream from digestion. Many type 2 diabetic ultimately require insulin. This happens because insulin production eventually drops below a threshold level as a result of the body not producing enough insulin, or not using the produced insulin properly.

The greatest risk factor for type 2 of diabetes is obesity. Treatment for this disease includes weight loss via attention to a healthy diet and cardiovascular exercise.

There are compelling reasons to avoid diabetes

As discussed, diabetes is a very serious disease. In this section we examine the additional difficulties diabetics face. The purpose of this section is to give the classroom teacher the necessary background to motivate students to make lifestyle choices, which may keep them from getting sick.

Type 2 diabetics generally begin their disease in poor health, and then suffer serious long-term debilitating diseases. Diabetics have an elevated risk of kidney failure, heart attack, stroke, nerve damage, major circulatory problems, and blindness. Any diabetic that lives for long, thanks to life-saving insulin, is very likely to have additional substantial health problems.

People with Type 2 diabetes may be unaware of their progressing disease for years. They typically develop insulin resistance, and once diabetes is diagnosed, oral medications to stimulate the islet cells to produce more insulin may be given. These drugs are called Sulfonylureas and Meglitinides.

Thiazolidinediones (TZD) also helps diabetics use their own insulin properly. Other pills can slow down the absorption of sugar and starch (Alpha-Glucosidase Inhibitors). Glucophage drugs reduce the amount of sugar the liver releases. These are all possible medications to be given before a diabetic is given insulin injections.

If blood sugar levels cannot be managed by oral medications, insulin injections may be provided by syringes, insulin pens, or insulin pumps.

Diabetic nephropathy is the medical name for kidney disease. Almost half of all kidney failure in the United States is a result of diabetes. (6) With kidney failure, diabetics may need to spend up to 12 hours per week going through dialysis. This may be done in the hospital, or at home. Either way, it is a severe limitation.

Diabetes raises risk of heart attack. A diabetic has the heart attack risk profile of a person 15 years older. (7) The risk of stroke is two to four times higher for diabetics. (8)

Diabetics frequently suffer from peripheral neuropathy, the symptoms for which are tingling and decreased sensation in the feet. This can lead to sores on feet, as the diabetic does not sense they are wearing a poorly fitting shoe. Such minor injuries can lead to major problems such as in infections and amputations.

Diabetes can also cause damage to vascular blood vessels that affects blood flow and circulation of blood to the arms and legs. Poor blood supply can also lead to poor wound healing and ulcers, in later stages of the disease. Diabetics can also suffer from impotence.

Diabetic retinopathy is the leading cause of blindness in U.S.

The history of insulin research

Although diabetes mellitus has been known since Egyptian times, very little treatment existed until the early 1920's. Historically, diabetic patients were put on a starvation diet, essentially limiting carbohydrates and sugar. This diet would avoid a spike in blood sugar. There was little the medical profession could offer patients. Most diabetics died young.

In 1921 Fredrick Banting and Charles Best (working under the supervision of professor John MaCleod of the university of Toronto made a pancreatic extract from one dog and injected it into another dog which had had its pancreas removed. This extract reduced the high sugar level in the blood of the diabetic dog. This insulin extract was tested later on humans and similar results were obtained. (9)

The success of this treatment resulted in the awarding of the Nobel Prize in medicine to Fredrick Banting and John MaCleod in 1923 (Banting shared part of his prize money with Charles Best). They made the patent for insulin available, and so insulin production was available worldwide.

In 1955, insulin was the first protein to be sequenced by British biochemist Fredrick Sanger, for which he won the Nobel Prize in Chemistry. Three years later it was the first protein to be chemically synthesized.

In the early days (1920-1982) insulin extracts from cows and pigs provided insulin to millions of people suffering from diabetes. As this insulin is not genetically identical to human insulin, it caused side effects in some patients. In 1982 recombinant DNA technology allowed *E. coli* bacteria to be genetically engineered to produce human insulin. Insulin is now molecularly exact, and diabetics suffer no immunogenic side effects.

Carbon Chemistry

Atoms

The periodic table lists all known types of atoms beginning with hydrogen at number 1 (one proton) and continuing to unstable synthesized atoms (with over 100 protons). The more important molecules involved in life processes are carbon (6 protons), hydrogen (1 proton), oxygen (8 protons), nitrogen (7 protons), phosphorous (15 protons), and sulfur (16 protons).

Atoms and their Interactions

Atoms are the fundamental particles that make up all matter. They combine (via several kinds of chemical bonding) to form compounds. A compound is a substance with two or more elements, combined in a specific ratio. Water is an example; it has two hydrogen atoms and one oxygen atom.

The chemical activity of atoms is determined by how full the outer electron shell of the atom is. As well as listing the atomic numbers (the number of protons), the periodic table organizes atoms by the available spots they have in their outer electron shells for more electrons. In order to fill these openings, atoms will receive, donate or share electrons.

Oxygen, carbon, hydrogen and nitrogen compose over 96% of the human body's weight. Insulin has the chemical formula $C_{257} H_{383} N_{65} O_{77} S_6$. The numbers in subscript indicate how many each of the named atoms goes into this molecule.

Covalent and hydrogen bonding

In covalent bonding, two atoms share outer electron shell electrons. Molecules are atoms that are held together by covalent bonds. The shape and charges on the outside of molecules is very important to their biological activity.

Water is a molecule with important chemical properties for living things. The two hydrogen atoms are held tightly to the oxygen atom by covalent bonds. It is a polar molecule, which means the electrical charges are not distributed equally around the molecule. The oxygen end of the molecule is slightly more negative, and the region of the molecule around the two hydrogen atoms is slightly more positive. This feature of water makes it very useful for this molecule to dissolve solutes. The differing charges at the ends allow the water molecule to surround and isolate the solute particles. In fact, water is called the "universal solvent".

Oxygen, carbon, hydrogen and nitrogen and sulfur make proteins.

Hydrogen bonds are very weak bonds that result from the interactions between the slightly positive end of the hydrogen atom and a slightly negative end of a molecule. Water atoms hydrogen bond with each other. This feature allows water molecules to adhere to each other, a feature called water cohesion.

We will also see the importance of hydrogen bonding when we look at the DNA molecule in our transcription and translation sections. It is hydrogen bonding which holds the double stranded molecule of DNA together.

Protein chemistry

Atoms combine to make small molecules such as glucose or amino acids. Some small molecules are monomers that combine via covalent bonds with other monomers to make larger molecules called polymers. In living systems, there are four main groups of polymers: lipids, carbohydrates, proteins and nucleic acids. We will consider the latter two in detail.

There are billions of different kinds of proteins in the natural world. They are all built from among the twenty amino acids, and it is the sequence of these amino acids, their primary structure, which is the first step in the protein's individuality. There are eight essential amino acids which humans must obtain from our food, as we cannot assemble them ourselves. These are tryptophan, lysine, methionine, phenylalanine, threonine, valine, leucine, and isoleucine.

Amino acids are molecules that are composed of an amino group (a molecule composed of nitrogen and hydrogen), a central carbon, and a carboxyl group (a molecule of carbon, oxygens and hydrogen). Located off the central carbon atom is an R group. The R group is a molecule that makes each amino acid different from the next, and what is responsible for the specific chemical activity of each amino acid.

These amino acids are linked together to form protein polymers by means of dehydration (condensation) reactions. As the name of the reaction suggests, a water molecule is released when the carboxyl end of one amino acid is linked to the amino group of the next amino acid. This creates a peptide bond that is a strong chemical bond between amino acids. This is why protein molecules are also called polypeptides.

When the amino acids bonds are broken by digestion or other chemical process, a hydrolysis reaction must happen, which involves adding a water molecule to the end of each amino acid.

Proteins have a secondary structure that is dictated by the arrangement of hydrogen bonds between the ends of the amino acids. Depending on the arrangement of these hydrogen bonds, the protein may fold into a sheet or helical formation.

The tertiary level of structure is very important to the overall function of the protein. The overall three-dimensional folding, generally a result of interactions among the R groups of the individual amino acids, results in a molecule that has a shape to meet its functional needs. Insulin, for example, facilitates transport of glucose into the cell by docking to receptors on the surface of the cell and causes a change in the cell membrane, which permits glucose to enter.

Insulin is composed of two chains, an A and B chain. The A chain has 21 amino acids, the B chain has 30 amino acids. Two disulphide bonds link this polypeptide, another disulphide bond is formed in A chain. The disulphide bonds occur between cystine amino acids on each chain, and there is a third disulphide bond which links part of the A chain back on itself.

There are many good images of this molecule on the internet, such as those on these pages.

http://www.expasy.org/spotlight/back_issues/sptlt009.shtml

http://www.pharmaceutical-technology.com/projects/eli_lilly/eli_lilly1.html

Transcription

DNA, like protein, is a polymer. It is linear, with a double-helix formation, and is constructed from nucleic acid monomers. DNA stands for deoxyribonucleic acid. It is the molecule that can be thought of as the blueprint from which all proteins are assembled. This important molecule is stored in the nucleus of eukaryotic cells (this is a cell type with membrane-bound organelles such as the nucleus, ribosomes, mitochondria, chloroplasts, and, in green plants, chloroplasts). In prokaryotic cell such as bacteria, it is loose in the cytoplasm of the cell.

DNA has several important structural elements. The double strand is held together by two sugar-phosphate backbones. Attached to these backbones are nitrogenous bases. These bases (adenine, guanine, cytosine, and thymine - abbreviated A, T, C, and G) are the language used by the cell to transfer information from one generation to another, as well as provide the instructions for making proteins. The bases pair in a specific order: A with T and C with G.

Although all genes are present in a cell's DNA, only certain genes are expressed in a given cell. The biochemistry of cellular activity determines when protein products are needed, and under these conditions the cell initiates the process of making proteins.

The genes in the DNA can be thought of like the cookbook for living things - it has the recipes for making all proteins. Just like recipes, and proteins, some are long, others short. To carry the analogy further, each sequence of nucleotides is like a recipe, and each three base codon is like an ingredient.

RNA stands for ribonucleic acid, and like DNA, it is a nucleic acid polymer. It differs from DNA in that it is single stranded, has a ribose sugar in the backbone (instead of a deoxyribose sugar) and uses uracil (U) instead of thymine (T). RNA does not remain in the nucleus of the eukaryotic cell; it is a copy of the DNA that leaves the double-membrane bound nucleus and travels to a cellular organelle called the ribosome. The ribosome can be thought of as the cell's protein factory.

When a cell is in need of a particular protein product the DNA is transcribed. Transcription is the process by which the genetic code on DNA is copied to the RNA, specifically messenger RNA (mRNA) that then carries this message to the ribosome.

Translation

The "Central Dogma" of modern biology simply says that DNA codes for RNA that subsequently codes for a sequence of amino acids - a protein, also called a polypeptide.

At the ribosome, the cellular organelle responsible for making proteins, the mRNA is read, and transfer RNA (tRNA) brings amino acids from the surrounding cellular matrix to the site. This is how a peptide (protein) molecule is built.

In the case of insulin, the molecule is ultimately composed of strands A and B. Strand A is composed of 21 amino acids, strand B is composed of 30 amino acids. There is a third strand that initially links A and B, called C that is made of 34 amino acids. The C strand is not a functional part of the final insulin molecule, and it is snipped off the larger continuous molecule after it is translated.

Insulin production

The genetic sequence of insulin was worked out early as a result of figuring out the amino acid sequence, then working back to the genetic code. When this code was known, it was then possible to take advantage of recombinant DNA technology to insert the gene into a bacterial cell.

When insulin from other living things is examined, it is apparent that all insulin molecules are not equivalent. When looking for human insulin substitutes to inject into humans, cow and pig insulins were found to only differ by three and one amino acid respectively. These insulins were purified and used as "semisyntheic" or "humanized" insulin. The supply of this insulin was insufficient, it was expensive, and difficult to purify. Additionally, while the insulin initially functioned properly, patients' immune systems would frequently produce antibodies against the foreign insulin.

The development of recombinant human insulin in the 1980's has been a major improvement to the treatment of diabetes. The gene that produces insulin is located on chromosome 11 of humans and was successfully inserted into the K-12 strain of *E. coli* bacteria.

Evolution of insulin

When learning evolution in high school, we generally examine the morphological results of the changes in the genetic code (Galapagos' finches beaks, for example.). Evolution of molecules is an especially fascinating topic as it brings evolutionary principles closer to the chemical source of diversity. In the classroom lesson section there are suggestions for using online databases of molecular sequences for various organism's protein chains to explore evolution of insulin across taxa.

Long before mammal evolution, or even vertebrate evolution, insulin evolved. It appears to have been a chemical messenger *among* bacterial cells indicating food was available in the general area. It later became the molecule responsible for regulating organismal blood sugar.

Different species do not have identical amino acid sequence, but the location of disulphide bonds, both ends of the A chain, and other features allow the protein molecule to assume the same conformation so it can perform the same job.

Diversity is generated by variations in the genetic code. Amino acids in the protein molecule may substituted as a result of mutations to the DNA. While these are subtle differences in the insulin molecule, the functional regions remain unchanged. However, in the case where these mutations caused the insulin to be nonfunctional, the organism did not live to pass on this mutation. In other cases, the mutation resulted in a change that did not have a deleterious effect on the function of the molecule. In this case, the mutation remained with the organism and may be passed on to the next generation.

Classroom lessons

Build molecular models

Students unfamiliar with basic chemistry should begin by reviewing a periodic table. There are a variety of tables to choose from to download and print out at this site http://www.sciencegeek.net/tables/tables.shtml. Use the table to help students understand the role atomic number and electrons play in simple molecule formation.

Diatomic oxygen, carbon dioxide, water, and methane are great models to begin with. If the classroom does not have access to a molecular model kit, you may allow students to use colored gumdrops (black = carbon, blue = hydrogen, etc.) and toothpicks to assemble these molecules. Another option is to purchase a variety of bolts and nuts. Different style nuts (hex, square, brass, wing nuts, etc.) and different lengths of bolts can be used to model molecules and chemical bonding.

To extend this model, protein manufacture can be done as a construction activity. Students can be provided with a three letter RNA codon that would have a complimentary match (A to U, C to G) to an amino acid. Making up all the codes for the entire protein would be a job for the entire class to engage in. Students could then use the materials to simulate transcription and translation. This would be a useful tactile approach which would help students better grasp the steps of transcription and translation.

A method to simulate this with students in the classroom would be to use children's snap toys with adhesive velcro added to simulate hydrogen bonding. Also, as a demonstration, the teacher could use a spray bottle to simulate condensation during connection of monomers.

Insulin evolution lesson

All animals use insulin, so why pigs (and not another animal source) is an interesting thought question for students to consider. Pig and cow/steer insulin was readily available, as many of these animals are raised for their meat. Have students discuss why neither squirrel, elephant nor starling insulin were chosen. Advanced students can learn about the different insulin forms by going to a protein data bank, such as http://ca.expasy.org/ (**Ex** pert **P** rotein **A** nalysis **Sy** stem) or http://www.ncbi.nlm.nih.gov/Structure/

Direct injection or mounted insulin pump is currently the only way to administer insulin. Have students discover why is this is the case. Students should investigate what happens in the digestive system to proteins that are ingested. Students can then explain why it is difficult to make insulin pill. (Digestion would break down the 51 amino acid polypeptide into the constituent amino acids and then they would need to be reassembled by the ribosome.) Can students think of other ways insulin may be delivered to the blood via the digestive system?

Insulin drug delivery

Insulin is also not a candidate for typical transdermal patch drug delivery as the molecule is so large (even though it is small by protein standards), and sufficient quantities could not be absorbed through the skin. Students could research the types of molecules that are delivered by patch, and compare and contrast these molecules with insulin. Students should describe the features of an insulin transdermal patch. The students should include the necessity of the patch to contact the bloodstream, how the dose would be managed, and how side effects could be managed. Other considerations to consider are cost, effectiveness, and patient comfort. What is the possibility of having an inhalable insulin system? (10) How about subcutaneous implantation, or transplantation of islet cells to the liver? (11)

The Ultimate Lesson

Modern medicine has been amazing in helping diabetics. Our students need to realize that avoiding diabetes is their responsibility. Middle school and high school is the time when our long-term habits are set down.

We need to help our students establish healthy ways of living. Students need to eat a healthy diet and get daily exercise. Frequently students do not recognize the long-term danger that comes from a diet of fast food, chips, and soda. We see much convenience food in schools, so can only assume this food is also eaten regularly outside of school.

The Rudd Center (http://www.yaleruddcenter.org/home.aspx) is focused on improving diet and preventing obesity. The Rudd Center has a blog, and regularly posts articles that deal with adolescents and food. If teachers and students were to visit this blog on regular basis and have discussions in the classroom, it may help begin to overcome the enormous pressures our students face in making healthy food choices.

A Healthy Lifestyle Plan

As many New Haven students are obese, this activity is one that should probably be done outside of the classroom, to reduce possible stigmatization.

As students react very positively to activities that directly involve them, students can calculate their own BMI (Body Mass Index). If students have Internet access, they can go to http://www.nhlbisupport.com/bmi/, if not, this is the formula:

BMI = (Weight in Pounds / (Height in inches) x (Height in inches)) x 703

Values over 25 are reason for concern, and weight loss should begin.

Students can then go to the Internet and calculate how many calories they need to eat in a day. http://www.wvda.org/calcs/

Students should then keep track of many they *really* are ingesting daily over the course of a week. Encourage students to keep a log of the calories they are taking in by reading labels and using online calorie counters.

Back in the classroom, students should be encouraged to reflect on their diet and possibly change their diet based on what they learned from their own personal inventory as well as class discussions about healthy eating. There is a wealth of helpful information at http://www.healthierus.gov/nutrition.html

Reading List for Teachers

Beekman M.J.H.I, et. al.. *Biotechnological Innovations in Health Care.* (Butterworth-Heinemann, London,1991)

Campbell, Neil A., Mitchell, Lawrence G., Reece, Jane B., (2000) Biology: Concepts and Connections, (San Francisco, CA: Benjamin Cummings), pp. 18-29, 42-47, 247, 526-527,

Saltzman, W.M., & Tran, V.V.. *Biomedical Engineering: Bridging Medicine and Technology.* In Press.

Teacher Resources - electronic

http://www.nabt.org/

The National Association of Biology Teachers is a tremendous resource for professional growth and classroom-tested lessons. Useful for grades 7 - university level.

http://www.nsta.org/

The National Association of Science Teachers offers science teachers excellent lessons and activities in their journals. All science disciplines are explored. Suggested for K-12 educators.

http://www.madehow.com/Volume-7/Insulin.html

This is a useful overview of the history and molecular structure of insulin.

http://topics.nytimes.com/top/news/health/diseasesconditionsandhealthtopics/diabetes/index.html?8qa

New York Times focus web site on diabetes. This offers an overview of the disease as well as recent New York Times articles on diabetes.

http://www.diabetes.org/home.jsp

American Diabetes Association

http://www.cdc.gov/diabetes/Statistics/

http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf

National Diabetes fact sheet, 2005. Much useful overview information.

http://www.littletree.com.au/dna.htm

Very good information on recombinant DNA technology

http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/pancreas/insulin_struct.html

On this site you can manipulate a molecular model of insulin.

http://en.wikipedia.org/wiki/Diabetes_mellitus

Very good overview of diabetes including molecular representations of insulin.

http://www.omhrc.gov

U.S. Office of Minority Health, division of Health and Human Services. This is a very useful site for data on how disproportionally diabetes affects African Americans and Hispanics.

http://www.genetics.com.au/factsheet/49.htm

Excellent background information on diabetes.

http://kidney.niddk.nih.gov/kudiseases/pubs/yourkidneys/index.htm

Detailed overview of kidney function.

http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm

National Diabetes Information Clearinghouse

Student Reading List

Melluish, B,. *Diabetes at 14, Choosing Tighter Control for an Active Life.* (Flower Press, United States, 2000).

Student Resources - electronic

http://www.thinklikeapancreas.com

Interactive site for kids with type 1 diabetes.

http://www.grandmasandy.com/books/MyOwnBookAboutPumping.pdf

An online book for younger students to explain the insulin pump.

DNA Fingerprinting http://www.pbs.org/wgbh/nova/sheppard/labwave.html

Simulation of molecular biology laboratory work.

http://www.cellsalive.com/cells/cell_model.htm

Excellent models of cellular function

Notes

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(1) Mark Saltzman 5/9/2006 seminar lecture

(2) May 16, 2006 NY Times, article accessed via:

http://topics.nytimes.com/top/news/health/diseasesconditionsandhealthtopics/diabetes/index.html?8qa

(3) http://www.usda.gov/cnpp/WP%20Obesity%20Article.htm

(4) http://www.nhps.net/about/demographics.asp

(5) June 27, 2006, Dr. Mark Saltzman seminar

(6) http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2005.pdf

(7) http://www.medpagetoday.com/Endocrinology/Diabetes/tb/3657

(8) http://www.kilorf.com/statistics.asp

(9) Beekman M.J.H.I, et. al.. *Biotechnological Innovations in Health Care.* (Butterworth-Heinemann, London,1991) p. 56

(10) http://journal.diabetes.org/clinicaldiabetes/v16n31998/pg140.htm

(11) http://www.medicinenet.com/script/main/art.asp?articlekey=52046

Implementing District Standards

(standards taken from http://www.state.ct.us/sde/DTL/curriculum/currsci.htm)

Standard 9.4 - Atoms react with one another to form new molecules.

In the chemistry section, there is a description of how atoms combine to form new substances by sharing electrons (covalent bonding). This is also modeled in the student simulation of DNA and protein molecule creation.

Standard 9.5 - Due to its unique chemical structure, carbon forms many organic and inorganic compounds.

The structure of the carbon atom plays a key role in the molecules we have examined.

The formation and structure of carbon-based polymers, including synthetic polymers, such as polyethylene, and biopolymers, such as carbohydrate have been explored.

Standard 9.6 - Chemical technologies present both risks and benefits to the health and well being of humans, plants and animals.

Simple chemical monomers can be combined to create linear, branched and/or cross-linked polymers for dialysis tubing, matrix in which islet cells can be placed.

The chemical structure of polymers affects their physical properties.

Standard 10.1 - Fundamental life processes depend on the physical structure and the chemical activities of the cell.

The general role of DNA and RNA in protein synthesis has been carefully considered.

Standard 10.3 - Similarities in the chemical and structural properties of DNA in all living organisms allow the transfer of genes from one organism to another.

In insulin production, the genetic information of bacteria has been altered to make them produce human insulin.

The benefits of altering the genetic composition and cell products of e coli to make human protein products have provided great benefit to humans.

Standard 10.5 - Evolution and biodiversity are the result of genetic changes that occur over time in constantly changing environments.

The minor molecular structural adaptation of insulin increases the chances for organisms to survive.