Metabolism

An Experiment on a Bird in the Air Pump Joseph Wright of Derby, 1768

In a previous presentation we followed studies of how the human body works up to the 17th Century. As the Scientific Revolution proceeded the old dogmas such as the humors were cast aside and experiments became the way to understand the processes of life. The painting shows the new scientific approach to understanding life. The scientist removes air from a glass container and shows that the bird can no longer live without air. The painting was based on one of the experiments conducted in by Robert Boyle (1627-1691) and published in 1660.

Oxygen in the air is essential to human life. Metabolism is the name given to the chemical reactions that occur in living organisms. It derives from the Greek *meta* (beyond) and *ballein* (throw) – it signifies the changes that are effected. It is composed of anabolism (ana, upward) – the production of new compounds – and catabolism (cato, down) – the breakdown of compounds.

From the Wikipedia notes on the painting
The witnesses display various emotions: one of the girls worriedly watches the fate of the bird, while the other is too upset to observe and is comforted by her father; two gentlemen (one of them dispassionately timing the experiment) and a boy look on with interest, while the young lovers to the left of the painting are absorbed only in each other. The scientist himself looks directly out of the picture, as if challenging the viewer to judge whether the pumping should continue, killing the bird, or whether the air should be replaced and the cockatoo saved. … To one side of the boy at the rear, the cockatoo's empty cage can be seen on the wall, and to further heighten the drama it is unclear whether the boy is lowering the cage on the pulley to allow the bird to be replaced after the experiment or hoisting the cage back up, certain of its former occupant's death. … The powerful central light source creates a chiaroscuro effect. The light illuminating the scene has been described as "so brilliant it could only be the light of revelation" (Kimmelman)

Although everyone remarks about the light in the painting, what is most intriguing to me is the darkness. This suggests that much of the science in the early days of the Scientific Revolution was stumbling in the dark. We discovered new ideas but we had difficulty understanding them

The Scientific Method

Francis Bacon (1561-1626)	Robert Boyle (1627-1691)	Thomas Sydenham (1624-1689)	Herman Boerhaave (1668-1738)

In his *Novum Organum Scientiarum* (1620), Bacon proposed that science should begin by careful observations, and then procced to the induction of general principles. He cautioned against any preconceived notions ("the idols of the mind"). These ideas set the stage for a century of observation.

Bacon's portrait is by Frans Pourbus the younger, 1614
Portrait of Boyle is by Johann Kerseboom , 1689
Sydenham's portrait is by Mary Beale, 1689
Boerhaave's portrait is by Cornelis Trost, 1735?

Novum Organum Scientiarum = new instrument of science.

In *The New Atlantis* (1627) Bacon imagined a group of philosopher-scientists who worked together in Solomon's House to discover new knowledge. This idea was put into practice when the Royal Society was founded in 1660.

For Bacon and his followers, experiments were more like experiences – what happens if? Lacking hypotheses they often led to the accumulation of facts without any organizing theory. Although careful observation is important, some imaginative prediction of what might occur is key to scientific discovery. Nowadays more attention is paid to hypotheses.

Boyle made important observations about pressure and gases and did derive Boyle's law that the pressure of a gas is inversely proportional to its volume. He also conducted multiple experimental observations on blood.

Two of the great clinicians of the time were Thomas Sydenham who practiced in London and Herman Boerhaave in Leyden. Both provided very clear and accurate descriptions of clinical diseases. Sydenham provided classic descriptions of chorea (a twitching on the limbs) and of gout. Scientific medicine was concerned with diagnosis. There were no effective treatments.

The Color of Blood

Drops of arterial and venous blood

Boyle conducted multiple experimental observations on human blood. He confirmed that the color of arterial and venous blood was different, a fact that had been reported by the physician Thomas Lower in 1669. He also examined blood's response to various alchemical analyses, described the difference in specific gravity between the dark red blood clot and the yellow serum. He knew that air was essential to life from his experiments with the air pump. Yet he was unable to see how the blood carried oxygen to the body. At that time oxygen had not yet been discovered (Priestley in 1774) and no one had yet seen red blood cells under the microscope (Jan Swammerdam, 1658).

We now know that the main function of the blood is to transport oxygen from the lungs to the tissues where it can react with nutrients absorbed from the gut to create energy. In the 17th Century we had no idea of what blood was or why it was so necessary for life. Galen's idea that blood was one of the humors was being treated with skepticism. Some wondered whether the blood might somehow contain vital spirits. Others wondered about the Christian ideas of being saved by the blood of the lamb.

Arthur Coga's Blood Transfusion 1652

In 1668, Richard Lower reported to the Royal Society that he had transfused the blood of a sheep into the vein of Arthur Coga, a patient who was mildly insane. The idea appears to have been that the blood of a gentle animal might calm Coga's tempestuous nature. Coga lived but his nature remained unchanged. Jean-Baptiste Denys had done the same thing in France the year before. Subsequent studies resulted in the death of several patients. The Royal Society banned the procedure.

This event illustrates the mindset of the 17th Century. Experiments were concocted to test ideas that nowadays would seem nonsensical. Transfusions of animal blood into a human being would usually cause a severe immune reaction in the recipient. This would result in hemolysis, kidney failure and death. The reason some of the early patients survived was either that they received only a small amount of blood or that most of the blood flowed interstitially rather than intravenously.

Transfusions between human beings are only safe if the blood types are compatible. Blood typing was discovered by the Austrian physician Karl Landsteiner in 1901 when he identified the ABO blood types. The Rh-factor was reported in the 1940s.

Occasional blood transfusions to replace lost blood during surgery were performed in the early years of the 20th Century. Blood banks and blood transfusions were used extensively during World War I.

L'Homme Machine

During the 17th Century scientists and philosophers began to think of the human body in terms of its physics and chemistry. In his *Traité de l'Homme* (1664) René Descartes proposed a simple mechanical explanation of the reflexive withdrawal from pain. The movement of the heat particles (A) pull on the thread (C) which opens a pore (de) which releases the animal spirits from the cavity (F) which then activate the muscles. These ideas culminated in the book *L'Homme Machine* published by Julien Offray de La Mettrie in 1747.

from the English translation of the *Traité;*
… if the fire A is close to the foot B, the small particles of fire, which as you know move very swiftly, are able to move as well the part of the skin which they touch on the foot. In this way, by pulling at the little thread cc, which you see attached there, they at the same instant open e, which is the entry for the pore d, which is where this small thread terminates; just as, by pulling one end of a cord, you ring a bell which hangs at the other end.... Now when the entry of the pore, or the little tube, de, has thus been opened, the animal spirits flow into it from the cavity F, and through it they are carried partly into the muscles which serve to pull the foot back from the fire, partly into those which serve to turn the eyes and the head to look at it, and partly into those which serve to move the hands forward and to turn the whole body for its defense

The *Traité de l'Homme* was written before 1633 but not published until after his death (1650) because Descartes was frightened of what had happened to Galileo who was condemned by the Inquisition in 1633.

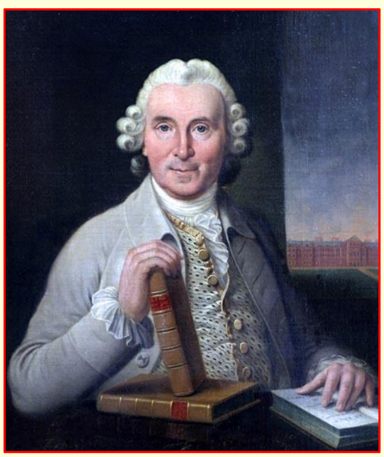
The idea of man as a machine meant that if one could figure out its mechanisms, one might be able to cure its ills. However, most ideas of how the human body worked were fanciful – "by pulling one end of a cord you ring a bell which hangs at the other end." Man was a machine but we had no idea how it worked. The first inkling came from attempts to cure or prevent the disease scurvy:

Scurvy

During the "Age of Exploration" from 1500 to 1800, approximately 2 million sailors died. On Vasco da Gama's 1498 voyage to India 116 out of 170 died; on Magellan's 1519 voyage round the world 208 out of 250 died. Most of these deaths were due to scurvy. The disease presented with bleeding gums, shortness of breath, muscle pain, and severe lethargy.

São Gabriel, flagship of Vasco da Gama on his voyage to India, 1498 painting by Luis da Camoes, 1880

In the painting the Gods look favorably on the ships. They were not so kind to the sailors.



Portrait by George Chalmers, 1750s?

James Lind (1716-1794)

Lind graduated from the University of Edinburgh and became a surgeon on HMS Salisbury. Many of the sailors suffered from scurvy. Lind conducted a controlled trial using 6 pairs of sailors, each pair treated daily with:

(i) cider
(ii) drops of vitriol (sulfuric acid)
(iii) vinegar
(iv) sea water
(v) two oranges
(vi) barley water

Only those given the oranges got better.

This was the first recorded "controlled" study. In assessing a treatment we must compare the treatment being evaluated to other treatments or to doing nothing. In modern pharmacology the goal is a double blind controlled trial. Neither the patient nor the person assessing them should be aware of whether the patient is taking the experimental treatment or the control. This design removes the problem of patients getting better simply because they think they should – placebo effect – and the problem of clinicians hoping that the new treatment works – observer bias.

Lind was aware of earlier reports that fresh fruit could prevent scurvy. However, as shown by his design, he was mainly thinking that this was due to the acidic nature of the fruit.

We now know that citrus fruit contain ascorbic acid – vitamin C. Although most animals synthesize this compound from glucose, primates are no longer able to do so and must ingest the compound in their diet. In the early evolution of human beings fresh fruit was readily available, and so we lost the ability to synthesize ascorbic acid.

This 1961 illustration of James Lind treating the patients with fresh oranges is by Robert Thom

Preventing Scurvy

Lind published his results in *A Treatise on Scurvy* (1753). In 1758 he was appointed chief physician at the new Royal Haslar Naval Hospital near Portsmouth, the largest hospital in England.

Lind realized that fresh oranges would not last through a long voyage and so he made a syrup by boiling oranges. Unfortunately heat broke down the ascorbic acid, and Lind's syrup was largely ineffective. It was not until 1799 that Gilbert Blane, another Scottish naval surgeon, convinced the British Admiralty to require its sailors to be given daily rations of citrus fruit juice. British sailors were thenceforth known as "limeys."

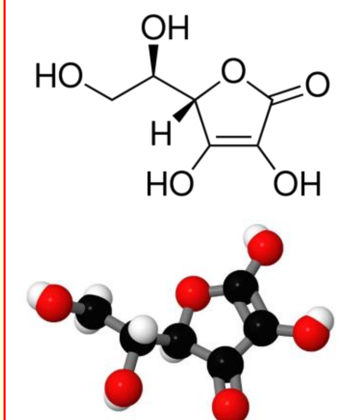
Of particular interest in this story was the 45 years between the initial proof that scurvy could be cured by citrus fruits and the final implementation of preventive measures. Vitamin C is much reduced by heating. Marmalade contains only tiny amounts of the vitamin. Another problem that undermined the evidence for citrus fruits was fraud. Sometimes naval vessels were sold dilute tartaric acid sweetened with lemon oil instead of fresh lemon juice.

One of the proposed treatments of scurvy that was tried by the navy was a syrup made from barley (“wort”). This was not effective against scurvy but did improve the health of the crews by providing vitamin B.

Gilbert Blane had connections in the aristocracy and was treated as a gentleman, whereas James Lind was a lowly ship’s surgeon.

Vitamins

Several compounds were found to be essential to human biochemistry. The name vitamin was initially proposed by the Polish biochemist **Casimir Funk** as “vital amine” in 1912. However, since not all vitamins are amines, the name lost its final ”e.” In 1916, **Cornelia Kennedy** first used the alphabetic nomenclature for vitamins A and B. In 1931 the Hungarian biochemist **Albert Szent-Györgyi** reported that the anti-scorbutic component of citrus fruit – vitamin C – was ascorbic acid. He received the Nobel Prize for this work in 1937.



Ascorbic acid is a necessary cofactor in several important biochemical pathways. Most important is the synthesis of collagen (connective tissue). Also important is its role as an antioxidant, detoxifying reactive oxidative radicals released from damaged tissue.

In his 2003 book on *Scurvy: How a Surgeon, a Mariner and a Gentleman Solved the Greatest Medical Mystery of the Age of Sail*, Stephen Bown wondered whether the British victory may have been in part due to the better health and morale of the British sailors due to a diet that included citrus fruit.

The painting is the Battle of Trafalgar by J. M. W. Turner, 1806. The dying Horatio Nelson lies by the mast. Nelson's victory over the combined French and Spanish fleets in 1805 marked the complete ascendancy of British naval power. For the next century no country could challenge Britain on the seas.

Beriberi

Beriberi (from a Sinhalese word for "weak") was a severe wasting disease, mainly found in Asia in the 19th Century. Takaki Kanehiro (1849-1920), a Japanese naval surgeon who had studied in London thought that this was due to a diet mainly limited to white rice. In 1884, he showed that a varied diet which included bread and meat reduced the incidence of the disease. The Japanese navy enforced the new diet but the doctors of the Japanese army believed that the disease was infectious, and refused to adopt the diet, with disastrous results. In the Russo-Japanese war (1904-1905), 27000 soldiers died from beriberi. Takaki was finally recognized for his work in 1905 and became known as the "Barley Baron."

Despite the problems with beriberi, the Japanese did win the war against Russia.

Thiamine (later known as vitamin B1) was identified as the essential dietary ingredient in the years around 1900 and Christiaan Eijkman and Frederick Hopkins received the 1929 Nobel Prize for this work. Takaki established the Jikei School of Medicine in Tokyo in 1881 – the location of the illustrated statue.

In the present, beriberi is mainly manifest as Wernicke-Korsakoff psychosis, characterized by confusion and memory loss. This is usually seen in alcoholics. Not only do they not eat a proper diet, the alcohol itself inhibits the uptake of whatever thiamine they do ingest.

Human Vitamins

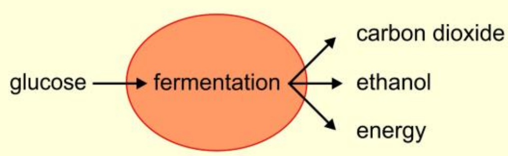
Vitamin	Source	Deficiency	Discovery
A (retinol)	carrots, oranges	night blindness	1913
B1 (thiamine)	meat, brown rice	beriberi	1910
B3 (niacin)	meat, fish	pellagra	1936
B12 (cyanocobalamin)	meat, fish	pernicious anemia	1948
C (ascorbic acid)	citrus fruits	scurvy	1920
D (cholecalciferol)	cod liver oil	rickets	1920

A vitamin is an organic molecule that is essential to the proper nutrition and growth of an organism and that must be obtained through the diet because it cannot be synthesized in sufficient quantities within the organism. The table lists only 6 of the 13 recognized human vitamins.

Enzymes

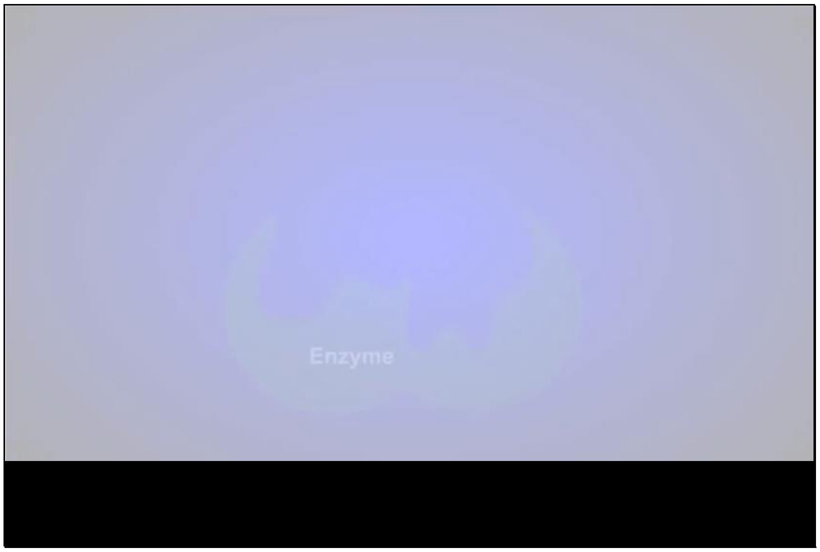
Nobel Prize photograph 1907

In 1897 Eduard Buchner (1860-1917), a German chemist, discovered that fermentation could be carried out by proteins extracted from yeast cells. These proteins were called enzymes (Greek "in sourdough"), a name that had earlier been used to describe the process of fermentation.

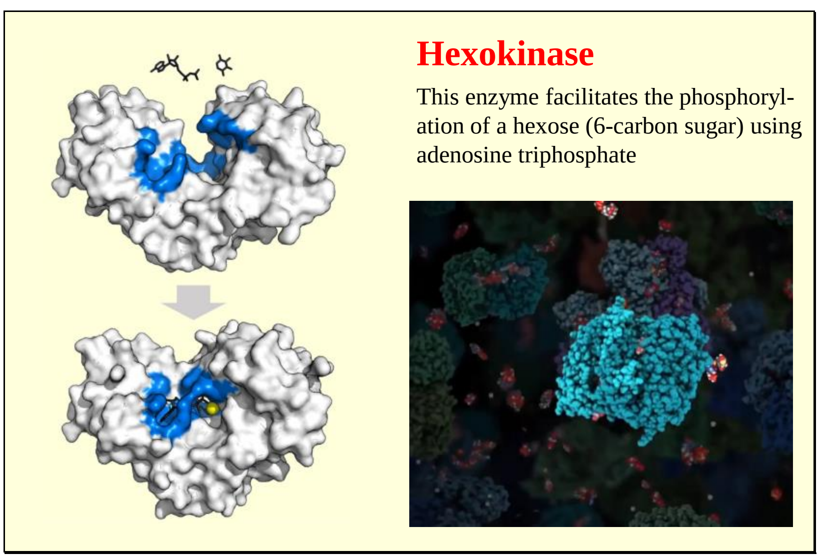


The breakdown of glucose to produce ethanol involves several enzymes. The glucose is broken down into two molecules of pyruvate and then these are converted to alcohol.

The enzymes in an animal cell are different and alcohol is not produced. When there is no oxygen the pyruvate molecules are converted into lactic acid. If there is oxygen the pyruvate molecules proceed through more complicated pathways to produce energy, water and carbon dioxide.



from Ricochet Science
https://www.youtube.com/watch?v=UVeoXYJlBtI

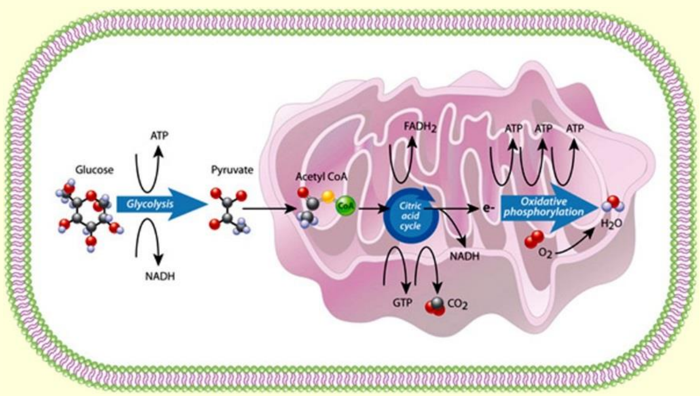


Video is a brief part of a longer and more complex video on enzymes:
https://www.youtube.com/watch?v=yk14dOOvwMk

In the diagram on the left the larger molecule at the top is adenosine triphosphate (ATP) and the smaller a hexose. Once located in the active sites (blue) of the enzyme and in the presence of a cofactor magnesium (yellow) a phosphorus atom is transferred from the ATP to the sugar.

The cytoplasm (inside of a cell) contains numerous different enzymes each facilitating a specific chemical reaction.

Cellular Respiration



Glycolysis occurs in the cytoplasm. The pyruvate atoms are then taken up into special organelles called mitochondria for oxidative phosphorylation

The processes in the mitochondria produce adenosine triphosphate molecules. These can then be used to provide energy for other cellular processes such as building new molecules, contracting muscles, etc.

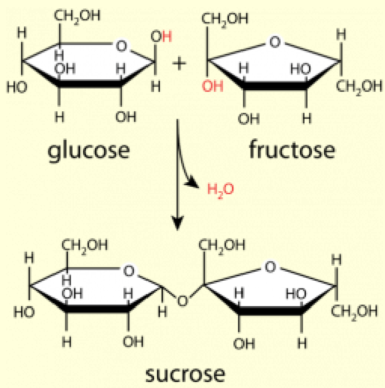
Glucose can be taken up from the blood or broken down from intracellular stores of glycogen (a large polysaccharide). Adenosine Triphosphate is a chemical that stores energy and can provide this for further chemical reactions when it converts to adenosine diphosphate (ADP. ATP has been called the currency of the cell – how it pays for things to be done. Nicotinamide adenine dinucleotide NAD is a co-enzyme that helps to facilitate reactions by removing electrons.

The major outcome of the mitochondrial metabolism is that multiple molecules of ATP are produced while oxygen is consumed and the pyruvate molecules are broken down to carbon dioxide and water.

The citric acid cycle is also known as the Krebs cycle after the German biochemist Hans Adolf Krebs who reported the complete cycle in 1937 and received the Nobel Prize in 1953. The Krebs cycle is "the metabolic heart of life" according to Nick Lane in *Life Ascending: The 10 Great Inventions of Evolution* (2009). The ten inventions are life (abiosynthesis), DNA, photosynthesis, cellular metabolism (Krebs cycle and other reactions), sex, movement, sight, hot blood, consciousness, death.

Glucose

The linchpin of human energy metabolism is glucose. Glucose is absorbed from the intestine after disaccharides and poly-saccharides are broken up by glycoside hydrolases. Glucose was isolated from grapes in the 18th century, but its chemistry was not studied until the work of Emil Fischer in the late 19th Century. Various tests to measure the level of glucose in the blood and urine were not available until the early 20th Century.



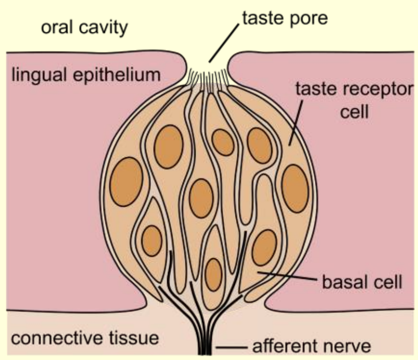
Glucose can be obtained from carbohydrates – starches and polysaccharides. The smaller carbohydrates molecules are known as sugars, although the term sugar often means sucrose.

Sugar Cane

Sugar cane was initially cultivated in India and South-east Asia 8000 years ago, and the juice was converted to sucrose over 2500 years ago. The Muslims introduced sucrose to Europe, but the plant required tropical temperatures. Columbus brought the plant from the Canary Islands to the Caribbean.

Sugar cane is refined to give sucrose by pressure to extract the juice and boiling to render the crystals. For centuries after Columbus arrival, the Caribbean islands were the major producers of sucrose. Nowadays, the major producers are Brazil and India. Sucrose is also used to produce ethanol which can be used as fuel.

Sweet Taste Receptors



Human beings have taste receptors in the tongue that respond specifically to sugars. These evolved because of the beneficial effects of recognizing and seeking out good dietary sources of glucose such as fruits. The availability of inexpensive pure sucrose led to excess consumption.

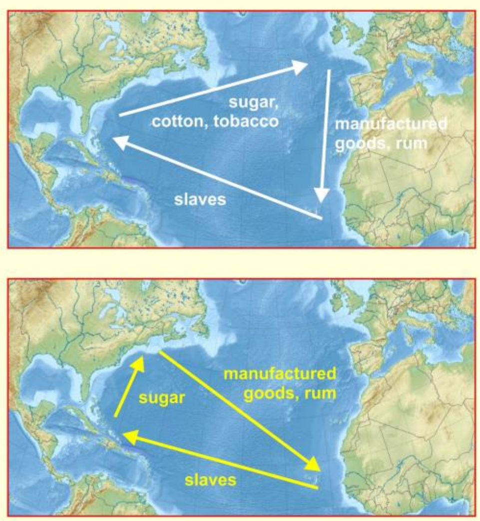
Before its production by slave labor in the Americas, sucrose was an expensive spice consumed only by the wealthy.

Sugar Trade

Sugar took Europe and the Americas by storm. Cooks competed to produce sweet desserts.

This led to tremendous health problems – dental caries became widespread, obesity proliferated, and diabetes mellitus became more common.

In addition, sugar was associated with the slave trade.

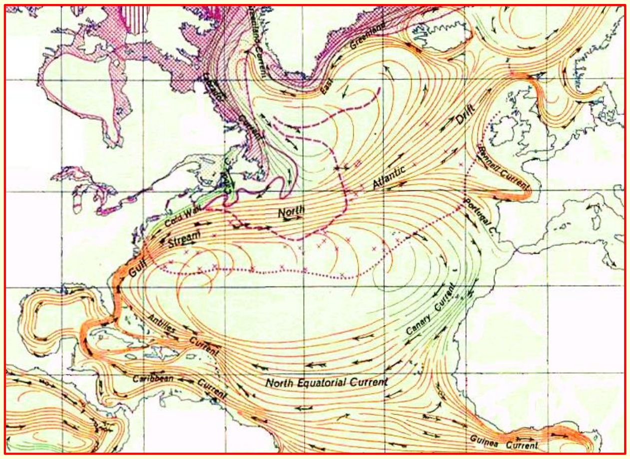


The cultivation and refining of sugar is backbreaking work in extremely got temperatures. For centuries sugar was produced in the Caribbean by slaves brought in from Africa.

The “triangular trade” is the term used primarily to describe the trading patterns depicted on the upper map. The lower map presents anther sugar-trading triangle, wherein sugar was brought to New England.

Sugar can properly be described as unhealthy and immoral.

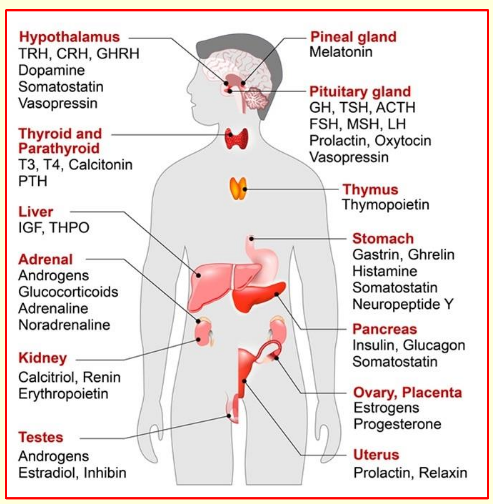
Winds and Currents



The trade routes in the North Atlantic were determined by the prevailing winds and currents. Travel to the Americas from Europe was easiest via the North Equatorial Current and the return journey via the Gulf Stream.

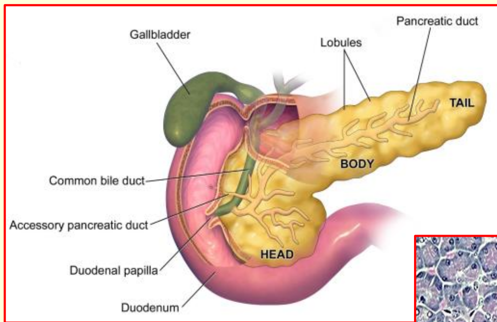
Hormones

Hormones are signaling molecules that control cellular metabolism. They are secreted into the blood by various glands in the body. Their secretion can be determined by other hormones, by serum constituents (e.g. glucose), or by nervous activation. They were first described in 1905 by Ernest Stahling, who had studied the hormones of the pancreas.



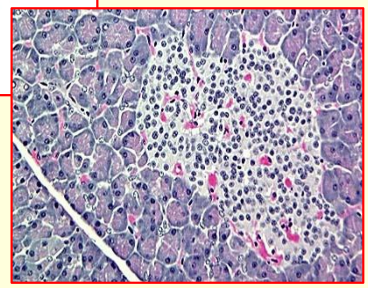
The word hormone comes from the Greek *hormao* to set in motion, urge on, excite, arouse.

The iodine-containing thyroid hormone thyroxine was the first hormone to be isolated in 1915. The scientist was Edward Kendall, an American Biochemist who worked at the Mayo Clinic Foundation. He received the Nobel Prize in Physiology for his later work on the chemistry of steroid hormones. Thyroxine increases metabolism in all cells of the body.



Pancreas

This gland, located below the stomach, secretes digestive enzymes into the duodenum.



In 1869 Paul Langerhans, a German medical student, described islets of cells in the pancreas that were not attached to the pancreatic ducts and appeared to secrete into capillaries.

In the histological ("study of tissue") section the Islets of Langerhans are seen as the lighter stained cells. Intermixed in these cells are multiple capillaries. The darker cells secrete into branches of the pancreatic duct. The term "insulin" comes from the Latin *insula*, island.

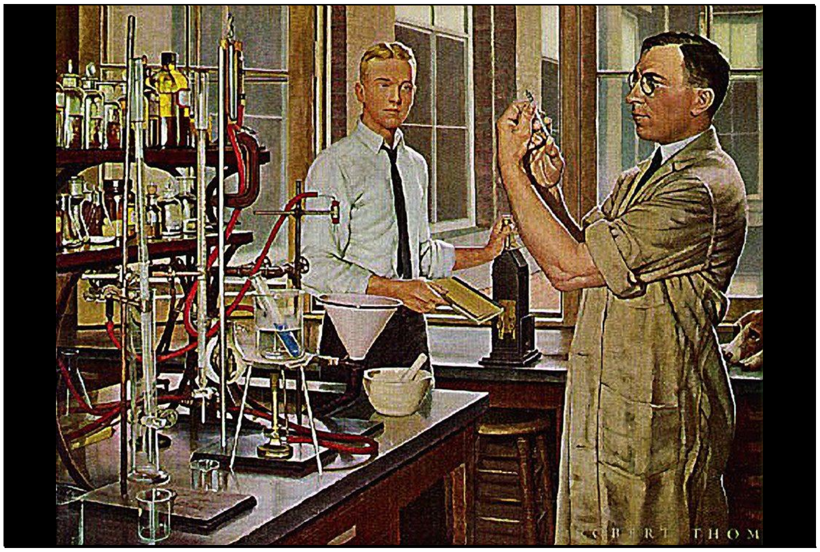
Discovery of Insulin

Diabetes mellitus (Greek, sweet siphon) is a disorder characterized by excessive urination with both the blood and the urine containing high levels of glucose. In 1889 Oskar Minkowski, a Polish physician, showed that removal of the pancreas in dogs caused diabetes. Several scientists attempted to isolate an anti-diabetic factor from the pancreas but the digestive enzymes in the pancreas rendered the extracts inactive. In 1920 Frederick Banting, a Toronto orthopedic surgeon, thought that he could prevent this by blocking the pancreatic duct. This would cause the secretory cells of the pancreas to become inactive, leaving only the islets of Langerhans.

Charles Best and Frederick Banting, roof of the Toronto Medical School, 1921

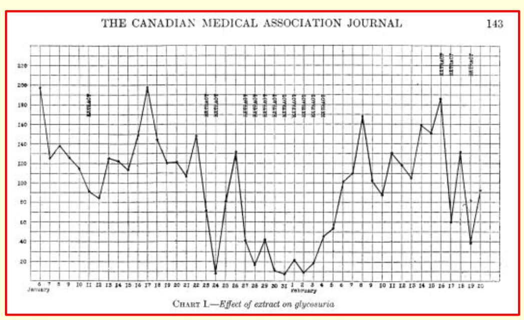
Diabetes is of two main kinds. Type I, which typically begins in children and is severe, is characterized by a loss of insulin secreting cells. Type II, which comes on in adulthood and is more chronic, is characterized by insulin resistance – insulin is produced but does not work as effectively as it should.

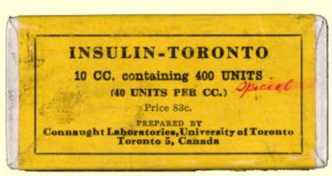
Banting took his idea to Professor J. J. R. Macleod at the Physiology Department of the University of Toronto. Macleod agreed to lend Banting some laboratory space over the summer of 1921 when he would be away on vacation in Scotland. He also provided some dogs and the help of a medical student Charles Best.



This 1961 depiction of Banting and Best is by Robert Thom. Note the dog on the bench on the right. Over the summer of 1921 Banting and Best were successful in isolating a pancreatic extract that could restore the normal blood glucose levels in the dogs who had had their pancreas removed.

In 1922 Banting and Best succeeded in controlling the levels of urine glucose in a 14 year old patient with diabetes.





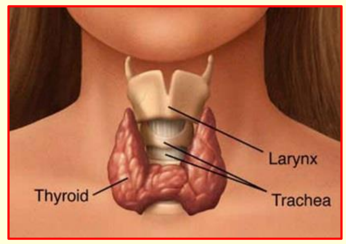
Production of insulin was carried out in the Connaught laboratories in Toronto

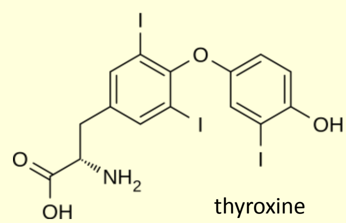
Banting and Macleod were awarded the Nobel Prize in 1923. Banting was upset that Best had not been recognized, and announced that he would split his part of the award with Best. Macleod reacted by splitting his award with one of the biochemists who helped to isolate insulin – James Collip.

There is much controversy about whether Macleod deserved the prize. He seemed to have done none of the actual research, though he helped to get the work published, came up with the name “insulin,’ and got the production of the hormone established at the Connaught Laboratories. Michael Bliss’s 1982 book *The Discovery of Insulin* provides much more detail than this brief presentation.

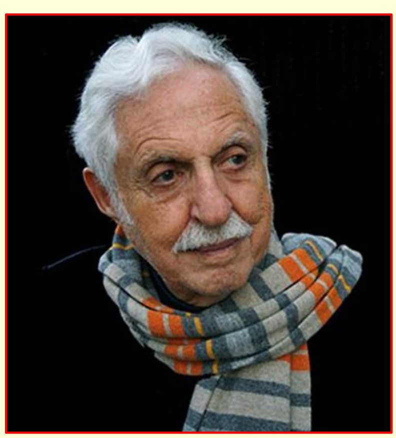
Thyroid Hormones

Jean-François Coindet (1774-1834) reported in 1820 that goiter could be treated with iodine. Later in the century, physicians began using thyroid extract to treat patients from whom the thyroid gland had been surgically removed. The iodine- containing thyroid hormone thyroxine was isolated in 1915 by Edward Kendall, an American Biochemist at the Mayo Clinic Foundation. Thyroxine increases the metabolism in all cells of the body. Too little results in tiredness and depression; too much causes hyperactivity and anxiety




thyroxine

Kendall received the Nobel Prize in Physiology in 1950 for his later work on the chemistry of steroid hormones. Thyroid deficiency can occur because of a deficiency in dietary iodine, congenital abnormalities in the metabolism of thyroxine abnormalities of the pituitary gland (which controls the thyroid), surgical removal of the thyroid, or an autoimmune disease (Hashimoto’s thryroiditis). Hyperactivity of the thyroid occurs in Grave’s Disease. This is characterized by weakness, weight loss, increased heart rate, irritability and bulging eyes.

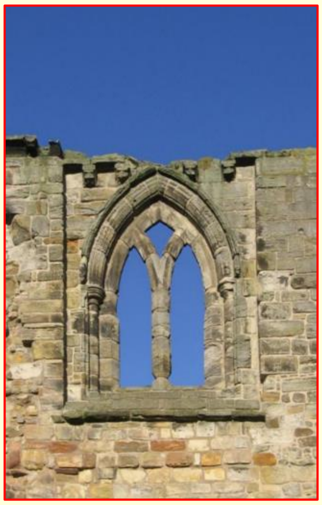

Carl Djerassi (1923-2015)
portrait by Karen Ostertag

Oral Contraception

In the normal menstrual cycle estrogen is secreted before ovulation and progesterone after. Progesterone inhibits ovulation. The first oral contraceptive – norethindrone, a progesterone analog – was reported by Carl Djerassi in the early 1950s. Marketing of this and other compounds began around 1960. The “pill” ushered in the “sexual revolution” of the 1960s.

Djerassi also wrote plays and science-fiction. One of his plays *Oxygen* (2001), written together with the Nobel Prize winner Roald Hoffmann, considers the discovery of oxygen as seen through the wives of Scheele, Priestley and Lavoisier.

Djerasssi amassed a large collection of artworks by Paul Klee, half of which were donated to the San Francisco Museum of Modern Art at his death.Djerassi was Jewish. Born in Vienna, he spent time in Bulgaria before moving to the United States in 1939. Bulgaria was unusual in the Eastern European Countries in its protection of its Jewish citizens.



High Windows

When I see a couple of kids
And guess he's fucking her and she's
Taking pills or wearing a diaphragm,
I know this is paradise
…
Rather than words comes the thought of
high windows:
The sun-comprehending glass,
And beyond it, the deep blue air, that shows
Nothing, and is nowhere, and is endless.

Philip Larkin , 1967

read by Tom Courtenay

The contraceptive pill made it possible for young women to have sex without fear of pregnancy. This new freedom led to the sexual revolution of the 1960s.

Larkin's poem *High Windows* provides a view of the sexual revolution. On the one hand he feels jealous of the new freedom. On the other he is deeply aware that there is more to life than fucking.

The whole poem:

When I see a couple of kids
And guess he's fucking her and she's
Taking pills or wearing a diaphragm,
I know this is paradise

Everyone old has dreamed of all their lives—
Bonds and gestures pushed to one side
Like an outdated combine harvester,
And everyone young going down the long slide

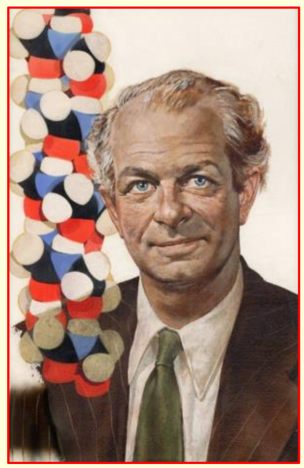
To happiness, endlessly. I wonder if
Anyone looked at me, forty years back,
And thought, *That'll be the life;*
No God any more, or sweating in the dark

About hell and that, or having to hide
What you think of the priest. He
And his lot will all go down the long slide
Like free bloody birds. And immediately

Rather than words comes the thought of high windows:
The sun-comprehending glass,
And beyond it, the deep blue air, that shows
Nothing, and is nowhere, and is endless.

Linus Pauling (1901-1994)

Educated at Oregon State University and the California Institute of Technology, Pauling's first major contribution was his 1939 book on *The Nature of the Chemical Bond*, which provided a new understanding of organic molecules based on quantum chemistry. Another important project was his 1949 demonstration of the two types of hemoglobin that occur in sickle cell anemia. In the early 1950s he published a series of papers identifying the alpha helix and beta sheet as prominent components of all protein molecules. He received the Nobel Prize in Chemistry in 1954. He became active in the peace movement and was awarded the Nobel Peace Prize in 1962.



Portrait with the Alpha Helix by Leon Tadrick, 1951

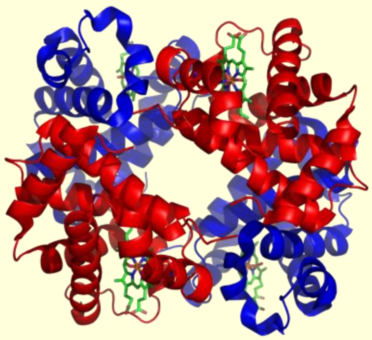
Because of his campaigning against nuclear weapons in the 1950s, Pauling was considered a communist sympathizer and his passport was transiently denied. Later in his life, Pauling became an enthusiastic proponent of the use of high doses of vitamin C to prevent disease, publishing *Vitamin C and the Common Cold* in 1970. This work has not been supported by carefully controlled trials.

Only four persons have been awarded two Nobel prizes. Linus Pauling is the only one not to have shared either prize. The three others are:
Marie Curie – 1903 Physics Prize with Pierre Curie and Henri Becquerel for radiation and 1911 Chemistry Prize for the chemistry of radium.
John Bardeen – 1956 Physics Prize with William B. Shockley for the transitor and 1972 Physics Prize for superconductivity.
Frederick Sanger – 1958 chemistry Prize for the synthesis of insulin and the 1980 Chemistry Prize for DNA coding.
https://www.bbvaopenmind.com/en/the-magnificent-four-who-received-the-nobel-prize-twice/

We started with blood and Boyle's observation of the color of arterial and venous blood. It is therefore fitting that we come to the end with some later discoveries about the workings of the red blood cells.

Hemoglobin

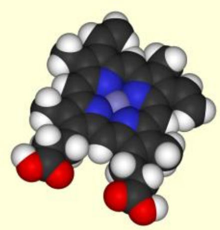
In the early 19th Century estimates of the molecular weight indicated that it was heavier than the hydrogen atom by a factor of tens of thousands. These results were initially considered nonsense. However in 1959 Max Perutz finally determined the molecular structure of hemoglobin using X-ray crystallography. The compound contains four protein subunits arranged in alpha helixes and four heme complexes that allow the transport of oxygen.

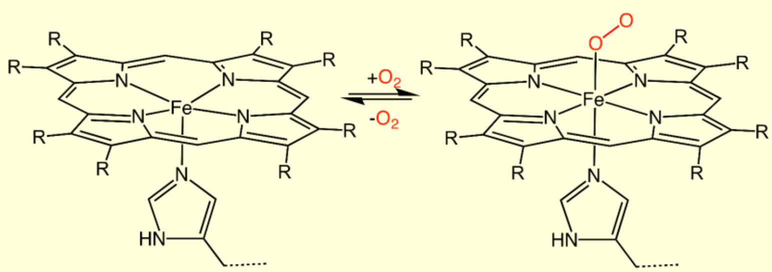


Model of Hemoglobin molecule: the protein subunits are shown in red and blue and the heme complex in green.

Heme

Each molecule of hemoglobin contains 4 heme complexes. These each consist of a porphyrin ring containing an iron ion. The iron atom can attract and hold oxygen for transport between the lung and the tissues.



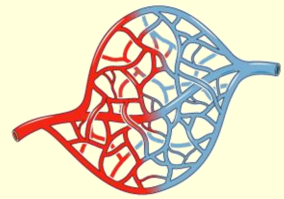


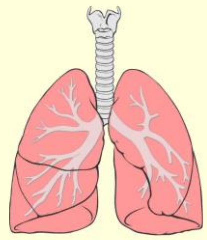
Carbon Dioxide can also be bound to hemoglobin. This binding occurs on regions of the protein chains rather than on the heme complex. When carbon dioxide is held by the hemoglobin it is called carbaminohemoglobin. When the carbon dioxide is bound to the protein the ability of the heme complex to bind oxygen is reduced.

Carbaminoglobulin has a bluish color. Oxyhemoglobin is bright red. These color changes are related to alterations of the porphyrin ring structure which change the way that it absorbs light.

Blood Oxygenation

In the tissues carbon dioxide is created during metabolism and diffuses into the capillaries. In 1904 Christian Bohr, a Danish physiologist, showed that this increased carbon dioxide caused the hemoglobin to release its oxygen so that it could be used in metabolism.





In the lungs the carbon dioxide diffuses into the alveoli (tiny air sacs). This causes the hemoglobin to release any carbon dioxide it is binding thereby becoming more capable of binding oxygen. This was shown by Christiansen, Douglas and Haldane in 1914.

The upshot of the "Bohr effect" and the "Haldane effect" is that hemoglobin transports oxygen from the lung to the tissues and transports carbon dioxide from the tissues to the lungs.

John Scott Haldane published many studies of human respiration. He is known as the father of oxygen therapy. He was the first to understand decompression sickness (the "bends") and the first person to provide gas masks to attenuate the effects of poison gas.

Both Christian Bohr and John Scott Haldane had famous sons. Emil Bohr was a famous atomic physicist; J.B.S Haldane contributed immensely to population genetics and evolutionary theory.

Sickle Cell Disease

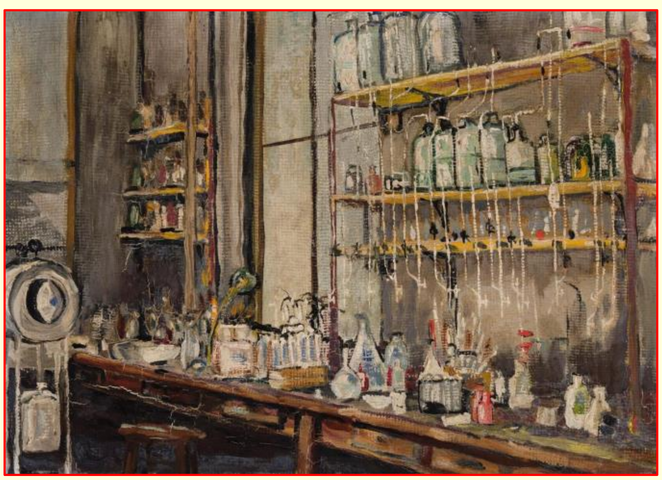
In 1949 Linus Pauling and his colleagues showed that this disorder is caused by an abnormal type of hemoglobin. They demonstrated that the hemoglobin in patients with sickle cell disease differed in the way it reacted to carbon monoxide. They also showed that relatives of these patients had both kinds of hemoglobin in their blood.

If a person has two abnormal genes ("homozygous"), the abnormal hemoglobin causes the red blood cells to become shaped like sickles rather than donuts. If a person has only one abnormal gene, both types of hemoglobin are present, the sickling is mild and the symptoms are minimal. However, this "heterozygous" version (sickle cell trait) makes the person resistant to malaria.

Sickle-cell disease was the first disorder to be attributed to an abnormal molecule and that first to show that such an abnormality can be caused genetically. The disease thus allows us to consider the basic concepts of inherited disorders.
1. the disease is caused by an abnormal gene that causes the blood cells to become shaped like sickles rather than donuts. This can block capillaries causing infarctions. The disease usually presents in childhood with attacks of pain.
2. during evolution the disease should have died out since people with the disease will not produce as many children as those without.
3. the disease is "recessive" – it requires two abnormal genes (one from each of the parents)
3. if there is only one abnormal gene, the hemoglobin is a little abnormal but not enough to cause severe symptoms - the person has "sickle-cell trait"
4. however, the hemoglobin in sickle cell trait makes the person resistant to malaria - the parasite cannot complete the part of its life-cycle that it spends in human red blood cells. This survival advantage ensures that the genetic abnormality persists in the population.

Linus Pauling's paper is the foundational paper for molecular medicine. It proposed the idea that an abnormality in a single gene could cause a disease and raised the hope that if we could someday alter the gene we could cure that disease.

Metabolism



The Lab, Frederick Banting 1925

This final slide shows Banting's painting of the laboratory wherein he and Best were able to extract insulin. Banting was a talented oil painter and later in his life went on painting trips with A. Y. Jackson. This particular painting was sold at auction in November 2018.

Chemistry Laboratories like this rapidly came to represent science in general.