frontiers | Frontiers for Young Minds

Behind a great medical drug there is always a great scientist!

Edited by
Fulvio D'Acquisto and Pasquale Maffia

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Behind a great medical drug there is always a great scientist!

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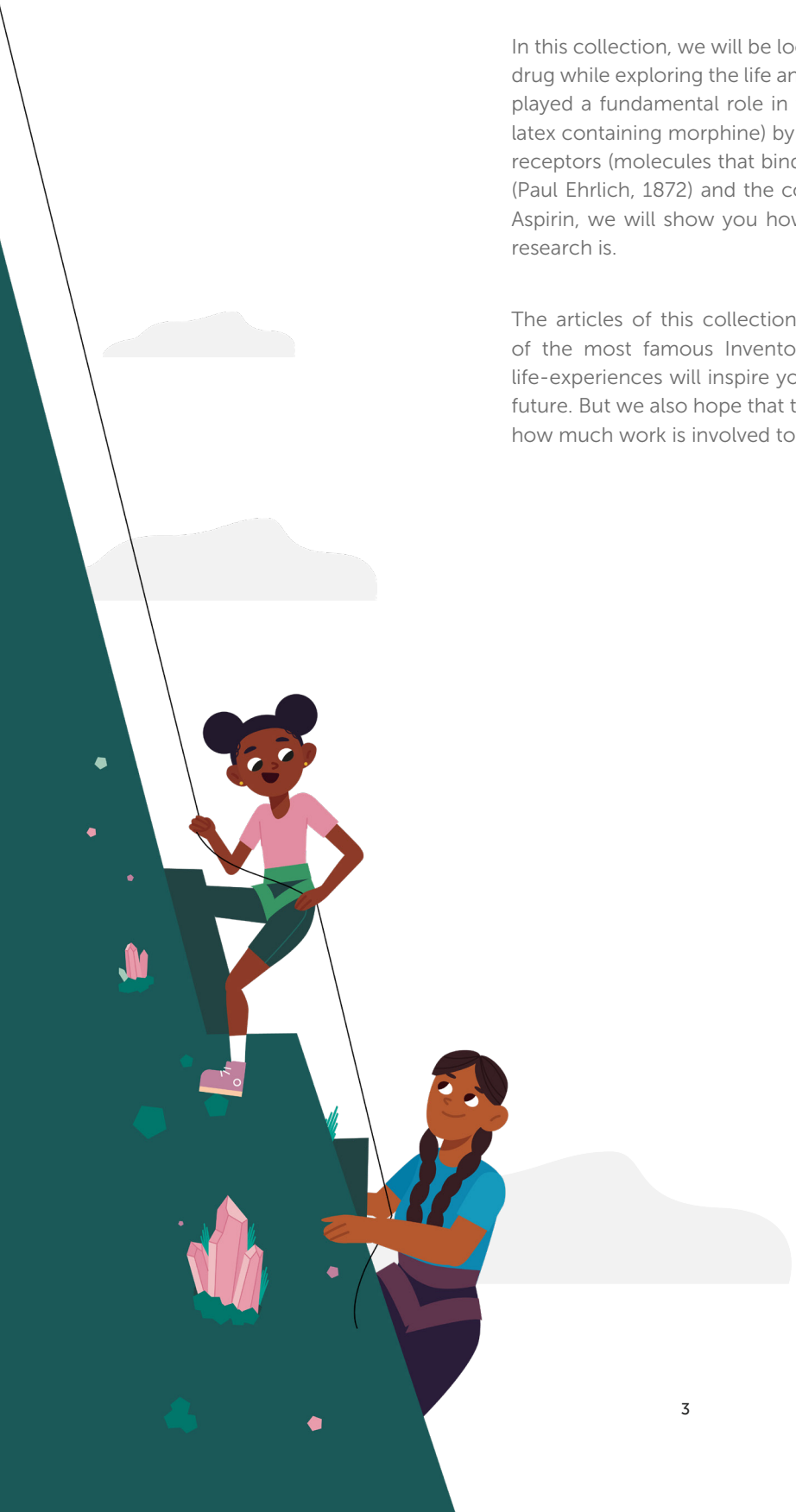
About this collection

Medical drugs are more than just compressed powder or bitter syrups. They are life saviour and one of the best rewards of a career in research. Did you know that behind any drugs there are amazing stories and incredible adventures of inspiring people that have dedicated their life to it?

In this collection, we will be looking at what does it take to discover a medical drug while exploring the life and journey of many scientists (and not) that have played a fundamental role in their creation. From the use of opium (a plant latex containing morphine) by the Sumerians in 5000 B.C. to the discovery of receptors (molecules that bind drugs) through colouring of biological tissues (Paul Ehrlich, 1872) and the contribution of Saint Aspren to the discovery of Aspirin, we will show you how fun, challenging and surprising the world of research is.

The articles of this collection will provide you with a very short biography of the most famous Inventors of today's medical drugs. We hope these life-experiences will inspire you to take a further dive in drug research in the future. But we also hope that this will make you realise how many people and how much work is involved to help us enjoy life to the full.



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SIR JAMES BLACK: THE MAN WHO CHANGED DRUG DEVELOPMENT

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YOUNG REVIEWERS:

CLASS 2B

AGE: 12

What is difficult about creating a new drug? In recent times, developing a new drug is based on understanding the specific processes of the disease the drug is meant to treat. However, this was not always the case. Drugs used to be discovered by a trial-and-error process, in which chemists tinkered with chemicals and hoped for success. How did we move from that inefficient method to the method we use today? Sir James Black is the father of two important medicines, propranolol (to treat high blood pressure) and cimetidine (to treat stomach ulcers). By focusing on what was causing those diseases, Black helped to transform drug development into the modern, efficient process we have today. How did a boy who came from a mining community in Scotland grow up to become the father of modern drug development? Keep reading to find out!

INTRODUCING JAMES BLACK

Taking medicines to relieve our symptoms or make us better is one of the most common things we do when we are sick. But did you ever stop to think about how new medicines are developed in the first place? The process is very different—and much more efficient—now than it used to be years ago!

Early drug development was based on the effects of natural products, such as using the natural pain-relieving properties of willow bark to develop aspirin. Back then, scientists did not have a deep understanding of how diseases developed. Therefore, figuring out whether a natural product worked against a certain disease was basically a process of trial and error—not a very efficient way to develop new medicines [1]! Over the years, scientists gained a better understanding of diseases, and that helped them to create new medicines that target specific pathways of the disease they are trying to treat [1]. Compared to older medicines, newer ones can provide patients with better treatment, with minimal side effects. But how did scientists get from a trial-and-error approach to specifically targeting disease pathways?

Enter, James Black

James Black grew up in a mining community in Fife, Scotland. Following his older brother, he studied medicine at the University of St. Andrews. After his graduation in 1946, he decided not to practice medicine and instead started his research career under Professor Robert C. Garry [2]. His research focused on investigating substances absorbed by the intestines and their effects on blood pressure. His time doing research had a positive impact on the rest of his career.

Black's scientific journey was not a smooth one. He traveled the world for a few years and eventually became a lecturer in physiology in Singapore. While there, he continued to investigate the relationship between blood flow and absorption of medicines through the intestines. The unique cultures that Black encountered in Singapore helped him appreciate how different mindsets can lead to new methods of tackling problems.

Black returned to London in 1950 but had trouble finding a job. On one fateful day, he bumped into his old professor, Professor Garry, on Oxford Street on his way back from an interview [2]. To support his former student, Professor Garry arranged for Black to set up the Physiology Department at the University of Glasgow's Veterinary School. As Black built the department, he also studied how a **hormone** called **adrenaline** affects the human heart. This paved the way for his future success, as you will soon see.

HORMONE

Chemical signals released by cells that control many of the body's responses.

ADRENALINE

A chemical that controls part of the body's nervous system and is responsible for the fight or flight response, causing the heart to beat faster.

A CAREER FULL OF TWISTS AND TURNS

While at the University of Glasgow, Black built his career by turning his research ideas into medicines. However, his career took many twists and turns and was not considered the normal academic path. He switched between working for universities and drug-manufacturing companies several times, which helped him to build a bridge between the two areas.

One of the companies he worked for was called Imperial Chemical Industries, where he was highly successful. There, Black helped develop **propranolol**, a drug used to manage irregular heartbeats [2]. He later moved on to work as the head of biological research at SmithKline and French (now known as GlaxoSmithKline). While there, he investigated the effects of **histamine**, a substance involved in the immune response, and developed a medicine called **cimetidine**, which stops the production of stomach acid.

Black then switched back to academic research, accepting a position at University College London as a professor in pharmacology. But he missed working in industry, where it was easier to see the results of his research. Finally, he got his dream job King's College London, where he was able to conduct academic research for industrial applications—the best of both worlds! Black's path through both industry and academic research allowed him to build a remarkable career in drug development.

PROPRANOLOL

Medicine used to treat high blood pressure and prevent heart problems from getting worse. Part of the beta blocker class of medications.

HISTAMINE

A chemical that is part of the body's defense system and is also involved in the production of stomach acid.

CIMETIDINE

Medicine used to treat heart burn and stomach ulcers by stopping histamine activity in the stomach.

FIRST BREAKTHROUGH—A DRUG TO SLOW DOWN THE HEART

Black's focus on treating heart disease led to his first breakthrough in drug development—a medicine called propranolol [3]. Before propranolol was developed, treatment for heart diseases such as angina and high blood pressure were not always effective. Angina causes discomfort in the chest area, and high blood pressure can negatively affect multiple body systems. Individuals with high blood pressure are at a greater risk of heart failure.

Many bodily processes are controlled by chemicals called hormones. Adrenaline is a hormone that causes the heart to pump harder. To do so, it must stick to molecules called **receptors** on the surface of heart cells. Prior to this discovery, scientists did not know how adrenaline could cause the heart muscle to contract and relax. The American scientist Dr. Raymond Ahlquist was the first to suggest that the effects of adrenaline were controlled by two receptors, alpha and beta, that cause different responses in the heart muscle [3]. Black was strongly influenced by Ahlquist's theory, and he worked on trying to decrease the workload of the heart.

RECEPTORS

Structures on the surfaces of cells that can turn certain cell functions on or off based on whether a molecule binds to them.

At that time, heart disease was treated by increasing the amount of oxygen transported to the heart. In contrast, Black's idea was to decrease the heart's need for oxygen by making the heart work less hard. **Beta blockers** are medicines that reduce blood pressure by blocking the effects of the adrenaline (Figure 1). This causes the heart to beat more slowly and with less force, and opens veins and arteries to improve blood flow, which lowers blood pressure [4]. Black's discovery completely changed the way doctors and researchers treated patients with heart disease, ultimately improving—and saving—many lives.

BETA BLOCKER

A class of medicines used to protect the heart by managing irregular heartbeats and blood pressure.

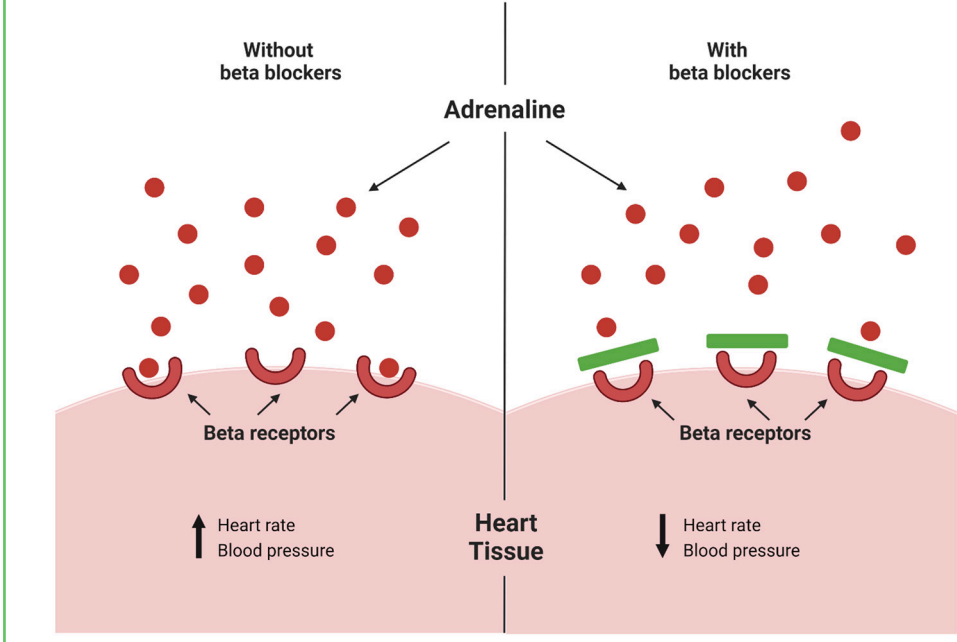

Figure 1

In the heart, the hormone adrenaline normally sticks to molecules called receptors on the surface of heart cells. One type of adrenaline receptor is called the beta receptor, and when adrenaline binds to this receptor it causes the heart to beat faster. Drugs called beta blockers (green bars) can block adrenaline from binding to the beta receptor, which decreases the workload of the heart and can help treat high blood pressure (Created with BioRender.com).

SECOND BREAKTHROUGH—A DRUG TO REDUCE STOMACH ULCERS

Black's second groundbreaking discovery was a drug called cimetidine, which treats stomach ulcers [5]. Stomach ulcers are open sores in the lining of the stomach and the intestines. The stomach normally produces acid to help digest food and to kill dangerous bacteria. The stomach has a mucous lining to protect it from acid damage. Ulcers happen when the protective layer of mucus is reduced, which allows stomach acid to eat away the tissues that line the stomach. Increased stomach acid can also affect the esophagus, causing heartburn.

PARIETAL CELLS

Cells located in the stomach that produce acid. Overactivity of these cells cause stomach issues like ulcers and heartburn.

Limiting the production of acid can help to treat stomach ulcers, and Black worked closely with his team of scientists to find a medicine that could block the production of stomach acid. Acid-producing cells in the stomach, called **parietal cells**, have receptors on their surfaces for a chemical called histamine. When histamine binds to this

receptor, it stimulates the parietal cells to produce acid. Black and his team identified the histamine receptor on parietal cells [5]. Cimetidine works by blocking histamine from binding to that receptor, stopping the acid-making parietal cells from responding to histamine, which decreases the production of stomach acid (Figure 2). This treatment can reduce the number and severity of stomach ulcers. The discovery of cimetidine helped to make stomach ulcers a treatable disease, rather than a disease that could reduce a person's lifespan.

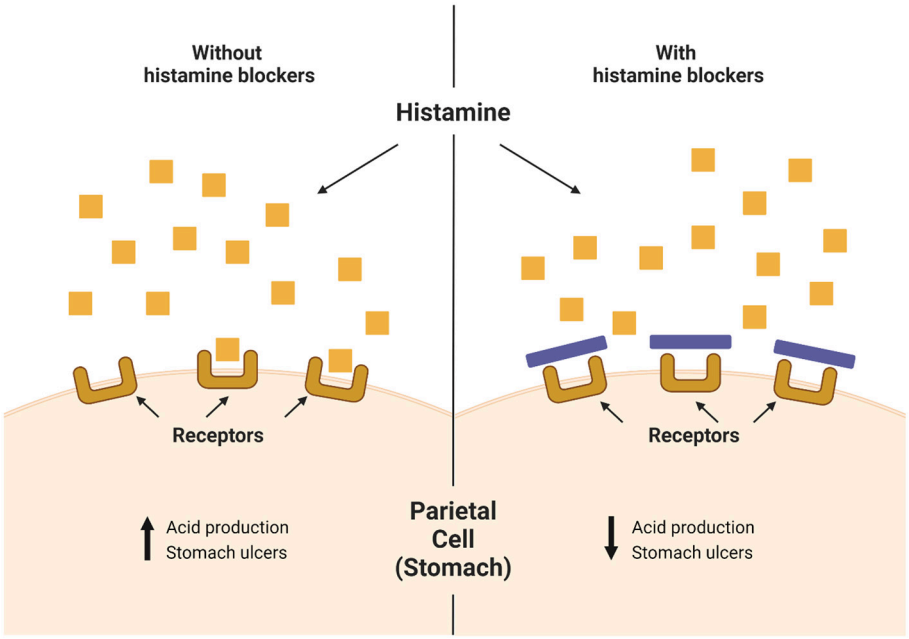

Figure 2

Figure 2

Parietal cells in the stomach normally secrete the stomach acid that digests food. Decreasing the amount of stomach acid produced is an effective way to treat ulcers. Normally, a chemical called histamine interacts with receptors on parietal cells and stimulates them to produce acid. Histamine blockers (purple bar) like cimetidine block histamine from attaching to those receptors, which decreases acid secretion (Created with BioRender.com).

CONCLUSION

The methods that Sir James Black used to create his medicines have changed drug development for the better. Propranolol and cimetidine revolutionized medical treatment of angina and stomach ulcers. Although these early medicines did have some side effects, his drug-development process helped other scientists to eventually create better medicines with fewer side effects. By providing knowledge about how receptors work and how to target them, Black helped to shape modern drug development.

Sir James Black's passion, curiosity, determination, and perseverance are an inspiration for anyone trying to achieve their goals. The two medicines he developed were among the most important contributions to medicine and pharmacology in the 20th century. For his groundbreaking work in establishing the backbone of the modern drug-development process, Black won the Nobel Prize in Physiology or Medicine in 1988.

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YOUNG REVIEWERS

CLASS 2B, AGE: 12

We are a group of fourteen 12-year-olds. Our favorite subjects are: maths, science, history, and also sports. We spend a lot of time together studying and playing after school. We also like to play and listen to music. We love all subjects, and we do a lot of projects! We always try to give our best!

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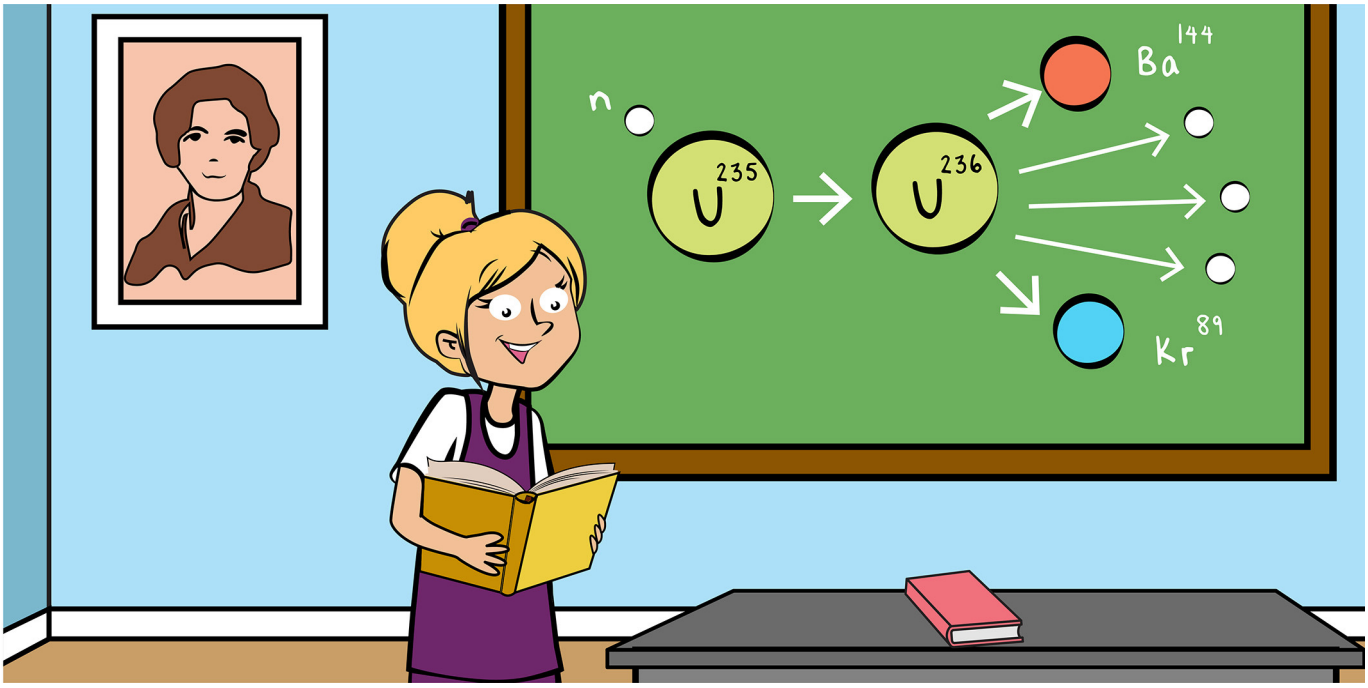

LISE MEITNER, THE SCIENTIST WHO CHANGED MEDICINE BY SPLITTING ATOMS

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MAYESHA

AGE: 12

The splitting of atoms, also known as nuclear fission, produces radiation and radioactivity. Dr Lise Meitner discovered how radioactivity could be produced in 1939. She found that firing a small particle called a neutron into another atom could cause radiation to be released. Radioactive atoms created in this way can be useful for detecting cancer or checking whether the body's organs are working properly. When radioactive atoms are injected into the blood of a patient, they travel through the body and release radiation that can be detected using special cameras, creating images or videos of the body's tissues. In this way, radiation helps doctors to better diagnose and treat patients. Unfortunately, Dr Meitner faced many obstacles and was never credited officially for her key discovery of nuclear fission.

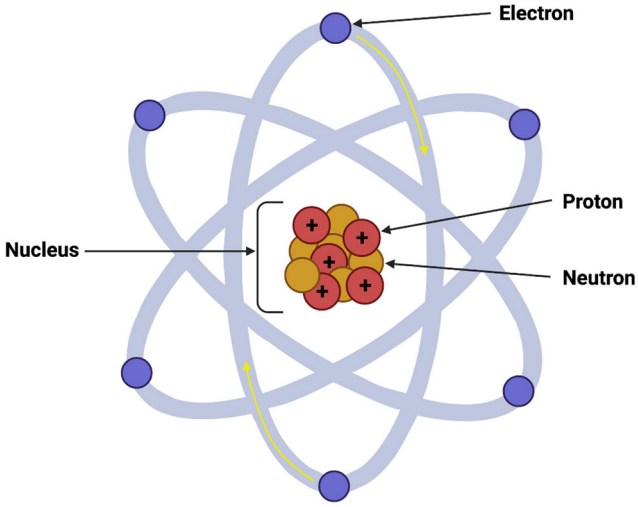

Figure 1

The structure of an atom. Atoms consist of a nucleus surrounded by negatively charged electrons. Protons (positively charged) and neutrons (no charge) are found within the nucleus (Figure created with BioRender.com).

ATOMS AND NUCLEAR REACTIONS

Everything and everyone we see in the world around us is made of tiny **atoms**. Within the center of every atom is the nucleus, containing even smaller particles called neutrons and protons (Figure 1). Negatively charged electrons constantly move around the nucleus. Electrons are attracted to protons in the nucleus, which are positively charged, similar to the way magnets are attracted to each other. Electrons also allow bonds to form between individual atoms, creating molecules [1][1]. Nuclear reactions refer to reactions that happen in an atom's nucleus. Nuclear reactions can produce certain kinds of energy or new radioactive atoms, which have many uses in medicine. These energies are known as **radiation**, because the energy "radiates" from the atom, just like heat radiates from the sun or a radiator to you.

ATOM

These are the small particles, containing a nucleus and electrons, which make up everything in the universe, including humans, food, trees, and buildings.

[1] For more information on Nuclear Physics, see http://nupex.eu/

RADIATION

The release of energy from a (radioactive) source in the form of waves, beams, or particles.

NUCLEAR FISSION AND RADIOACTIVITY

Radioactive atoms emit energy in the form of radiation. This energy is released because of an imbalance in the numbers of protons and neutrons in the nucleus, which makes the atom unstable. Releasing energy makes the atom more stable. So, radiation is energy released from unstable atoms in the form of high-energy particles or energy waves.

More than 100 years ago, Marie Curie famously discovered naturally occurring radioactivity. However, we now know how to make radioactivity using machines that fire neutrons into another atom. These machines, called nuclear reactors, cause **nuclear fission** reactions, which split the atoms and release radioactive energy and more neutrons (Figure 2). Meitner was a nuclear physicist whose research explained how unstable atoms produce radiation. Her

NUCLEAR FISSION

Splitting of an atom's nucleus into two lighter nuclei, simultaneously releasing energy in the form of radiation.

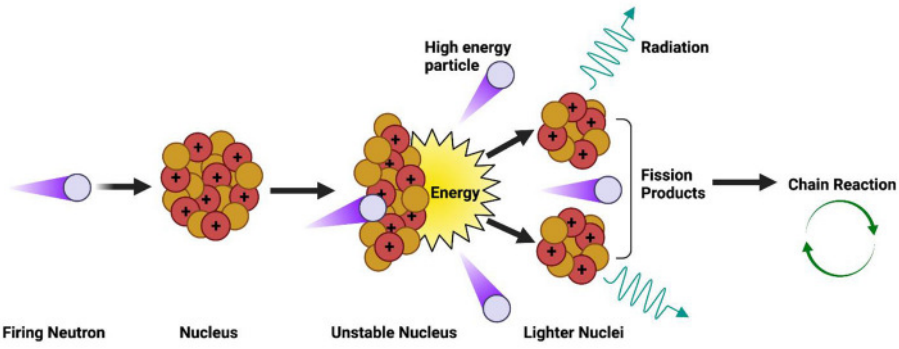

Figure 2

The nuclear fission reaction. When a fast-moving neutron is fired into the nucleus of an atom, the nucleus becomes unstable and splits into smaller parts, while also releasing neutrons and energy in the form of radiation. The fission products are atoms that can also become unstable and thus continue releasing radiation, in a chain reaction (Figure created with BioRender.com).

[2] For more information on Lise Meitner, see: https://www.sciencesmuseum.org.uk/objects-and-stories/women-physics

discovery of nuclear fission in 1939 led to developments in medicine that are still used today [2][2].

LISE MEITNER'S SCIENTIFIC CONTRIBUTION

In 1913, scientists already knew that the balance of numbers of protons, neutrons, and electrons within an atom affected its stability, and that radioactivity came from the nucleus. Dr Meitner and her colleague, German chemist Otto Hahn, were involved in the search for new radioactive elements. In 1918, they identified Protactinium-231 which is a radioactive atom called a **radioisotope** [3].

RADIOISOTOPE

A radioactive atom that has an unstable nucleus and too much energy, which it releases as radiation in the form of particles or waves.

While living in Sweden, Dr Meitner and her nephew Otto Frisch worked together to create a theory explaining the splitting of an atom's nucleus into smaller parts. They called the smaller parts fission fragments. They calculated the energy released and named this reaction nuclear fission. Despite all this work, the Nobel Prize for nuclear fission was awarded to Dr Meitner's old colleague, Hahn. He relied on Dr Meitner's knowledge of nuclear physics to make sense of his own chemistry findings. Sadly, as Hahn was first to publish these ideas, Dr Meitner and her nephew received little credit for the discovery [4].

RADIOISOTOPES FOR IMAGING DISEASE

The discovery of nuclear fission led to many medical advances (Figure 3). Radioisotopes enable doctors to perform medical **imaging** of the body, which helps them to diagnose and treat diseases. Radioisotopes are given to a patient either by injection or through food or drink provided at the hospital. As the radioisotope travels inside the body, special cameras outside the body can detect the radiation. This creates an image or video of the body's bones and soft tissues. For example, these images can tell us if a kidney is not working properly, but more than that, they can even tell doctors *which* kidney and also which *part*

IMAGING

This is when radiation is used in hospitals to take pictures of a patients' bones, organs, or teeth to understand more about what is going on inside the body.

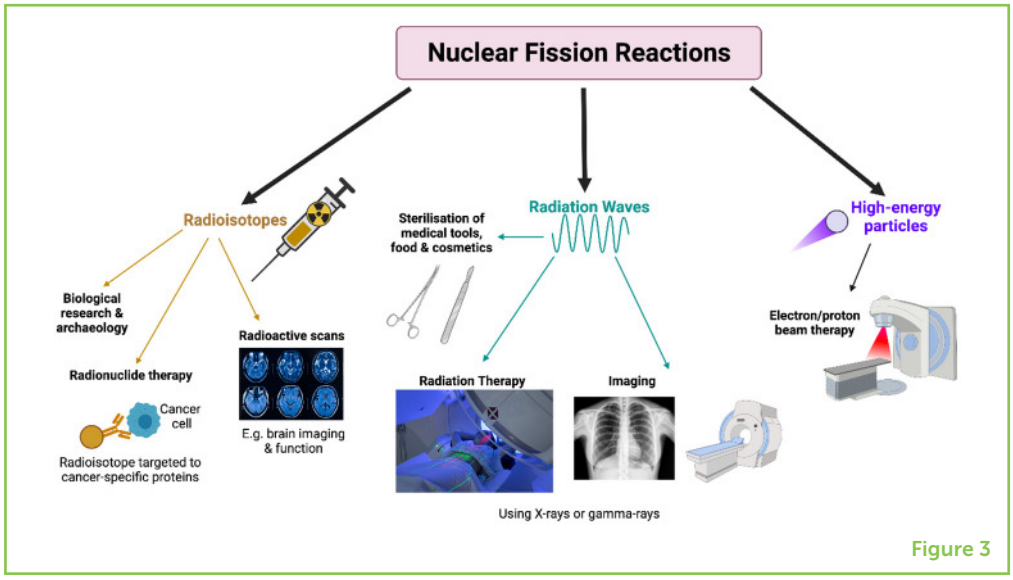

Figure 3

Figure 3

Nuclear fission reactions release various kinds of radiation, including radioisotopes, radiation waves, and high-energy particles, each with a variety of medical uses. Radioisotopes can be used in medical research, cancer treatment, and for medical imaging, which is useful for planning and monitoring therapy. Gamma rays can be used to sterilize medical tools for surgery or to decontaminate foods and beauty products to ensure they are hygienic. High-energy particles, such as protons and electrons, can be used as external beams, positioned to target, and kill tumor cells (Figure created with BioRender.com).

RADIOTHERAPY

The use of radiation waves, or beams of particles to kill unhealthy cells such as cancer cells in a patient.

of the kidney is malfunctioning. Medical images can also help identify the precise sizes and locations of cancers.

RADIOTHERAPY

Radiation can also be used to treat disease. This is called **radiotherapy**. The aim of radiotherapy treatment of cancer is to damage the DNA of the cancer cells. DNA is the code for all the building blocks, cells, that make up the body. By damaging DNA in a cancer cell, that cell no longer knows how to keep itself alive, so it dies. The result is reduced cancer growth or even complete elimination of the cancer. Doctors decide which type of radiotherapy to use depending on the size, type, and location(s) of cancer in the body. The treatment schedule is carefully planned by calculating the target area of the cancer, the amount of radiation needed, and the length and number of treatment sessions.

Most radiotherapy is delivered from outside the body, using a more sophisticated and powerful version of an X-ray. This is called external radiotherapy. However, certain radioactive sources can be used inside the body. This is known as internal radiotherapy. Just like for imaging purposes, radioisotopes used in internal radiotherapy are injected into a patient and travel around the body. However, the type of radiation used is different because doctors need to ensure that the radiation only travels a short distance within the body, so that no healthy cells are damaged. For this reason, particles called alpha and beta particles are used for internal radiotherapy, rather than X-rays. Also, radioactivity can be attached to certain compounds that carry the radiation to where the tumor is located. Internal radiotherapy using radioisotopes is very good at irradiating and killing tumors located in multiple sites within the body. This decreases the likelihood of the

cancer coming back. These kinds of tumors can not be treated with external radiotherapy.

OTHER USES OF RADIATION

Radiation is also used to sterilize the medical tools (needles, scalpels, and syringes) required for surgery (Figure 3). This is important to prevent germs from entering the patient's body. In food production, radiation is used to kill infectious microbes like salmonella. This helps foods to last longer without contaminating or changing them, like chemicals do. Radiation is sometimes used to control large numbers of pests, like mosquitos, by making them unable to breed.

THE OBSTACLES LISE MEITNER FACED

Lise Meitner was born in 1878, to a Jewish family of 8 children in Vienna, Austria. Being a woman in science was challenging at the time, but Dr Meitner managed to prove her worth in a male-dominated field. She built a successful career and made several breakthroughs for women. When she attended the University of Vienna in 1901, she was one of only four women allowed to join. She was only the second woman to be awarded a doctorate from the University in 1905[4]. In Berlin, when she worked closely with Otto Hahn at the Institute of Chemistry, Hahn found a space for her in the basement—even though women were not allowed in the building. After 14 years contributing to radioactivity research, Dr Meitner became the first female physics professor in Germany, 1926 [4]. She spent most of her life working in Berlin but had to flee from Nazi Germany in 1938 and moved to Sweden [4].

Albert Einstein called Dr Meitner the "German Madame Curie" because of her pioneering work. However, at the time, she did not receive the praise she deserved. Her experimental work was key to Niels Bohr's model of atomic structure, for which he received the full credit, with a Nobel Prize in 1922. Today, in many German museums, Dr Meitner's achievements are barely recognized, and she is almost invisible in all of Hahn's work and autobiographies. It is likely that the political situation at the time and Dr Meitner's escape from Nazi Germany as a Jew made it more difficult for Hahn to acknowledge their teamwork [4].

Despite the obstacles Lise Meitner faced during her career, she dedicated her life fully to nuclear physics. She never married and continued her work until the age of 81 [3]. Sadly, scientific discoveries can lead to unwanted consequences, such as the development of nuclear weapons. This deeply upset Dr Meitner, who turned down a job working on an atomic bomb with the British Scientific delegation [4]. Being a peaceful person, Dr Meitner would have been most pleased about the great medical achievements based on nuclear

fission. Dr Meitner retired in Cambridge (England) with her nephew and died in 1968, at the age of 90 [4]. In 1992, the element Meitnerium was named after her, to finally honour her contributions to nuclear science [5].

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YOUNG REVIEWER

MAYESHA, AGE: 12

Hi! My name is Mayesha. I am in 6th grade and 12 years old. I have one little cute sister. I am interested in scientific innovations and fictional stories. I love swimming and biking. I like to play legos and listen to stories. In my sparetime I spend a lot of time playing with my sister. My favorite subject in school is Mathematics.

AUTHORS

REBECCA DRAKE

I am a first-year RadNet City of London Ph.D., student, based at the Barts Cancer Institute, Queen Mary University of London, UK. My Ph.D., project aims to investigate how radiotherapy alters the growth and functioning of blood vessels supplying the tumor. I am using mouse models of breast cancer and 3D cell cultures to understand sensitivity to radiation, including the role of DNA damage responses within the cells lining the tumor blood vessels. Our overall goal is to overcome radiotherapy resistance by modulating signals produced by tumor blood vessels, in hope of improving treatment outcomes. r.j.g.drake@qmul.ac.uk

SAMANTHA Y. A. TERRY

I am a senior lecturer in radiobiology at King's College London, London, UK. There, I not only teach undergraduates and master's students about the use of radioactivity in imaging and treating disease, but I also run a research group that works in the lab determining how different types of radioactivity can be best used in the clinic. Questions we try to answer include: "Are radioisotopes used for imaging safe for healthy tissues?," "How can we make this radioisotope only irradiate cancer cells?," and "Is this radioisotope best at killing small or large tumors?" *samantha.terry@kcl.ac.uk

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I am a first-year RadNet City of London Ph.D., student based between King's College London and University College London, UK. My research focusses on assessing combinations of radiotherapy and immunotherapy to help treat head and neck cancers. I use a variety of techniques to examine the effects of different combinations to understand how we can best help patients. Our overall goal is to improve understanding of how these treatments work together and to use this knowledge to improve patient outcomes. sophie.langdon@kcl.ac.uk

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HUMAN HEALTH
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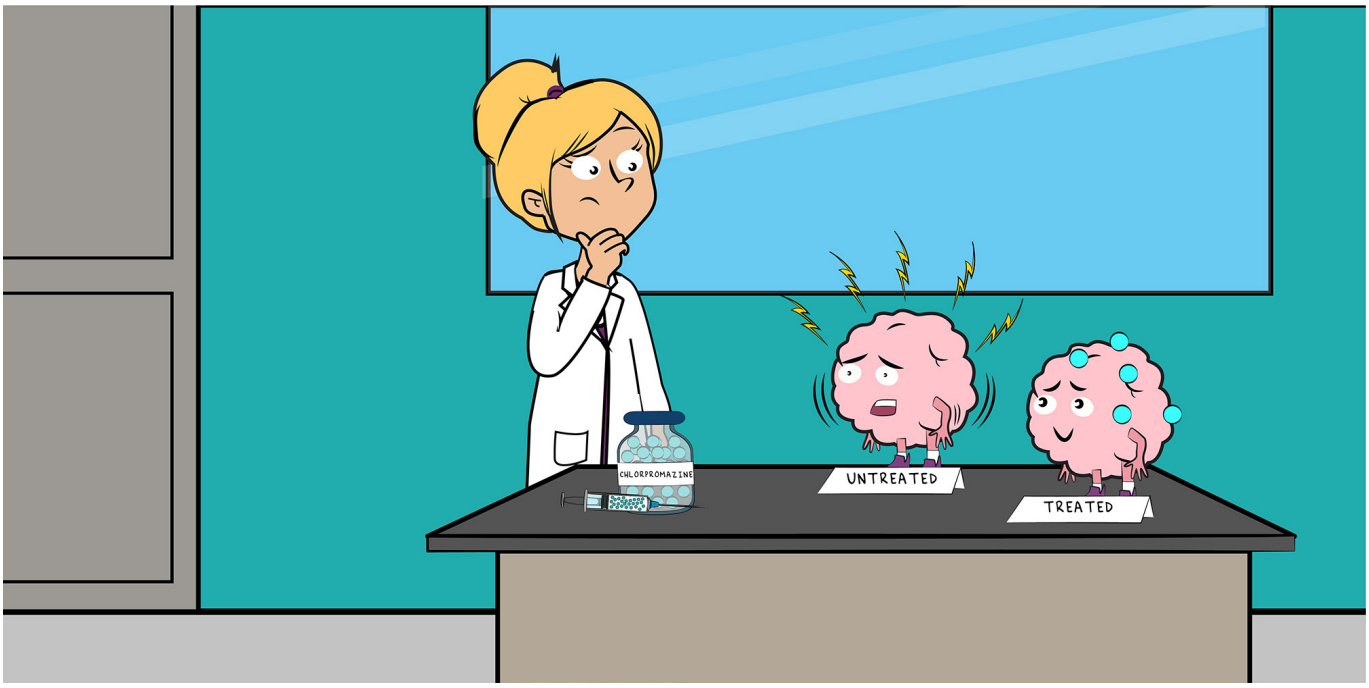

CHLORPROMAZINE: PAVING THE WAY FOR A BETTER UNDERSTANDING OF SCHIZOPHRENIA

Sandhra Sushilkumar[1], *Addison Claire Allen*[1] *and Nico Steel Osier*[2,3*]

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YOUNG REVIEWER:

ERIC

AGE: 12

Schizophrenia is a brain disorder that impacts quality of life and can require hospital treatment. Schizophrenia is thought to have affected humans throughout history; however, it was first described as a form of mental illness in 1887. Notably, doctors did not effectively treat schizophrenia until 1951, when Dr. Heinz Lehmann discovered that a drug called chlorpromazine could be used to relieve the symptoms of this disorder. Although chlorpromazine was initially used to keep patients asleep during surgery, researchers learned that it was also helpful for mental illnesses. While the causes of mental illness are still not completely understood, the discovery of chlorpromazine taught us a lot about how the brain communicates, and we learned that issues with communication between the brain and the body can lead to some of the symptoms of mental illness. Overall, chlorpromazine paved the way for future drugs and improved the lives of millions!

WHAT IS SCHIZOPHRENIA?

SCHIZOPHRENIA
A brain disorder that affects thinking, perception, emotions, or behavior.

DELUSIONS
False thoughts and scenarios.

HALLUCINATIONS
Perceiving things that are not there.

Schizophrenia is a serious mental health condition with symptoms including false beliefs (**delusions**), seeing or hearing things that are not real (**hallucinations**), and difficulty speaking. Schizophrenia has likely affected people for all of human history; however, it was not until 1887 that it was classified as a type of mental illness by Dr. Emile Kraepelin. In the past, people with schizophrenia often received mental health care only in special live-in hospitals, which meant patients were isolated from their families and friends. Early treatments were often dangerous, poorly researched, and would not be seen as responsible or safe by today's standards [1, 2]. These methods used chemicals or electricity to shock the brain and cause changes that could improve symptoms over time. Unfortunately, these treatments sometimes had severe side effects, like causing patient to go into comas. These extreme treatment methods were the only options, since medications were not yet available.

In 1951, the way we treat people with schizophrenia was forever changed. This was the year that scientists discovered the benefits of a drug called chlorpromazine for treating schizophrenia. Chlorpromazine was not only the first drug treatment for schizophrenia, but it was also the first medicine used to treat *any* mental health disorder! In this article, we will tell the story of how chlorpromazine was discovered, how it came to be used for mental health disorders, and how it paved the way for the medical field of psychiatry.

DISCOVERY AND TESTING OF CHLORPROMAZINE

Dr. Paul Charpentier always wanted to make surgery safer for his patients. In December of 1951, he helped create a new drug, named chlorpromazine (Figure 1). He gave chlorpromazine to a colleague, Dr. Henri Laborit, to test whether this drug could keep his patients asleep during surgery [3]. During Dr. Laborit's first time using the drug in surgery, he noticed it did not keep patients asleep longer, but it did make them calmer. Dr. Laborit reported this finding to one of his colleagues, Dr. Heinz Lehmann. This led Dr. Lehmann to wonder if chlorpromazine might be useful for patients with schizophrenia, since this condition causes irritation and restlessness [1]. The first person to receive chlorpromazine was a 24-year-old who suffered from many symptoms of schizophrenia, including hallucinations, delusions, and **agitation** [3]. The drug was injected into the patient daily. After 20 days, the patient's symptoms got better, and he was released from the hospital [3]! In 1952, news of these results spread rapidly and reached a hospital in Paris, where Drs. Pierre Deniker and Jean Delay decided to see these effects for themselves. By studying chlorpromazine in more people with schizophrenia, Drs. Delay and Deniker found that this drug *could* help reduce symptoms of schizophrenia [1]. Eventually, the

AGITATION
Restlessness and increased sensitivity to events.

Figure 1

Chlorpromazine was given to patients as an injection, to treat the symptoms of schizophrenia. The chlorpromazine molecule is comprised of many atoms: one sulfur (yellow), one chlorine (green), two nitrogens (purple), 17 carbons (black), and 19 hydrogens (blue).

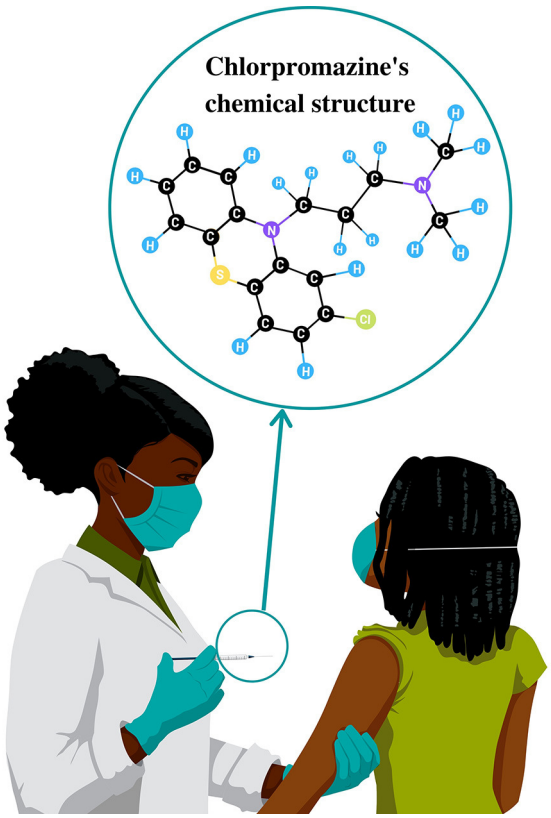

Figure 1

evidence was so strong that chlorpromazine was declared a worldwide success. Key events related to the development, testing, and success of chlorpromazine are summarized in Figure 2.

HOW DOES CHLORPROMAZINE WORK?

To understand how chlorpromazine works, we need to understand how this medication affects the brain and the signals that connect the brain to the body. Have you ever touched a hot surface? How did your body react? This is a perfect example of how the brain communicates with the body to help keep you safe. When you touch something hot, the cells of your hand sense the heat on your skin and communicate this to your brain. Your brain then sends a signal back to your hand, to pull it away quickly. This is an example of a process called **signal transmission**, which is the technical term for how the body and brain communicate. Some mental health disorders, including schizophrenia, are caused by too much signaling along important pathways. Specifically, people with schizophrenia have higher amounts of a substance called **dopamine** than the average person. Dopamine binds to proteins within the brain called **dopamine receptors**, which cause cells to communicate with each other through signal transmission. Increased dopamine signaling causes parts of the brain to become overactive, leading to the symptoms of

SIGNAL TRANSMISSION

The process by which the brain communicates with the rest of the body.

DOPAMINE

A chemical messenger used in brain cell communication that is elevated in people with schizophrenia.

DOPAMINE RECEPTOR

The location where dopamine binds normally and that chlorpromazine binds to lower dopamine signal transduction.

Figure 2

Historical events leading to the development and success of chlorpromazine.

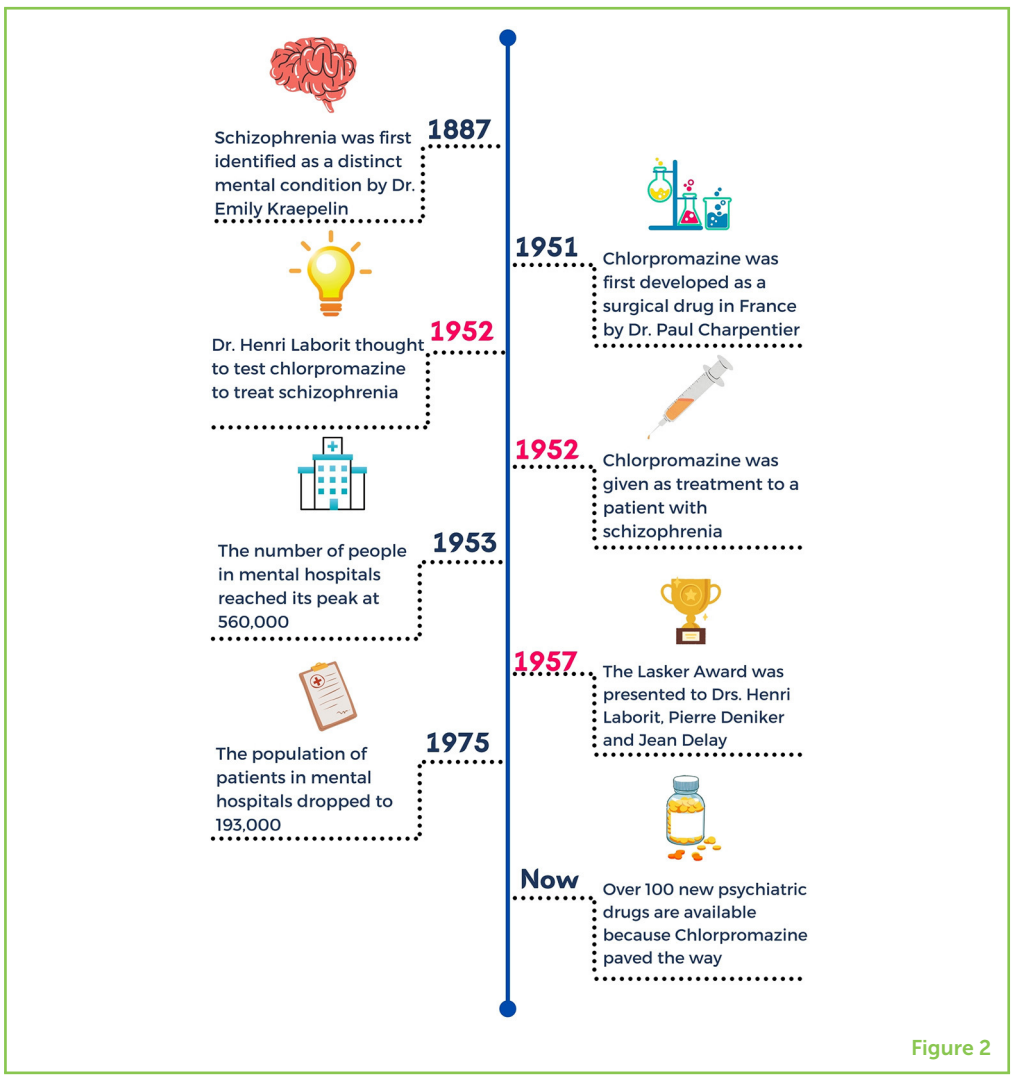

Figure 2

schizophrenia. Drugs like chlorpromazine bind to dopamine receptors, which blocks dopamine from binding and sending signals. Lower dopamine signaling reduces hallucinations, delusions, and other symptoms of schizophrenia. When chlorpromazine is taken for a while, it is very effective at reducing schizophrenia's symptoms. Each patient's symptoms are unique, so the amount of chlorpromazine needed and the amount of time patients must take the drug before seeing results can vary. Chlorpromazine helped scientists understand brain-to-body communication, which led to the discovery of many additional new drugs to treat other mental health conditions.

HOW DID CHLORPROMAZINE REVOLUTIONIZE PSYCHIATRY?

Ultimately, the effectiveness of chlorpromazine allowed patients with schizophrenia to be cared for in their homes, instead of in special hospitals. In 1953, around 560,000 patients lived in mental health hospitals, but by 1975, the number had decreased to 193,000 [2]. As

PSYCHIATRY

The study and treatment of mental, behavioral, and emotional disorders.

the first drug used to treat any mental health disorder, chlorpromazine played a huge role in establishing the field of **psychiatry**. Today, psychiatry is a special form of science and medicine used to study and treat mental health conditions. Building off what was learned from chlorpromazine, doctors of psychiatry now have over 100 different drugs to treat patients with mental health conditions [4]. Newer drugs have more benefits and lower risks than chlorpromazine, so today chlorpromazine is no longer the most common medication for schizophrenia.

By improving scientists' research on brain-to-body communication, chlorpromazine led to a better understanding of the brain, signal transmission, and a variety of mental health conditions, including depression and anxiety. Today, doctors and healthcare providers can choose the right treatments for patients based on their unique mental health conditions! This is wonderful because we now know that drugs work differently for each person. The goal is to treat all people safely, without any of them having bad side effects. Ultimately, because chlorpromazine brought so much awareness to the field of psychiatry, the American Public Health Association gave an award known as the Lasker Prize for Medicine to Drs. Henri Laborit, Pierre Deniker, and Heinz Lehmann [3]. Although it is not used as frequently to treat schizophrenia, 67 years after its first use, chlorpromazine is still considered an essential drug by the World Health Organization.

SUMMARY

In the past, mental health was not well-understood. Schizophrenia was first described as a form of mental illness in 1887 but, until the discovery of chlorpromazine, there were no medications available to treat this brain disorder. The discovery of chlorpromazine was a turning point in history, as it was the first drug treatment for a mental illness. This discovery helped the field of psychiatry to get started, as it showed that psychiatric illnesses can be treated with medication. Although it is not commonly used today, the discovery of chlorpromazine and its use for schizophrenia led to major improvements in the options available for treating mental health disorders.

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YOUNG REVIEWER

ERIC, AGE: 12

I am a seventh grader. I am a keen and passionate STEM student. I am also a music enthusiast who enjoys playing the piano and viola. I live with my parents, my younger sister and my pets. I like biology, physics, chemistry, and computer science. As a young reviewer, I feel deeply that scientists are the driving force behind human progress through Frontiers for Young Minds. I hope to become a scientist and help find cures to diseases.

AUTHORS

SANDHRA SUSHILKUMAR

I am currently an undergraduate student at The University of Texas at Austin. I am pursuing a Bachelor of Science and Arts in Biology, a minor in Iberian and Latin American Cultures and Health Professions certificate. After I graduate, I plan to obtain a Masters in Business Administration and attend dental school the following year. My favorite activities are dancing, yoga and cooking.

ADDISON CLAIRE ALLEN

I am a graduate from University of Texas at Austin with a degree in public health. Since I was a child, I have had an interest in how science can be used to improve

health care and treatment options. With a certificate in forensic sciences and health professions, I aspire to better the world through expanding our understanding of the human body and learning ways to better treat alignments.

NICO STEEL OSIER

I am a principal investigator at the University of Texas at Austin. I have bachelor's degrees in Nutritional Science and Nursing from Michigan State University, and a Ph.D., from the University of Pittsburgh. I love working with young scientists and empowering them to actively participate in research. To learn more about my laboratory visit my publicly available website: `https://nicoleosier.wixsite.com/osierlaboratory/` or follow @osierlaboratory on facebook, twitter, or instagram. In my free time, I enjoy traveling the world. *nicoosier@utexas.edu

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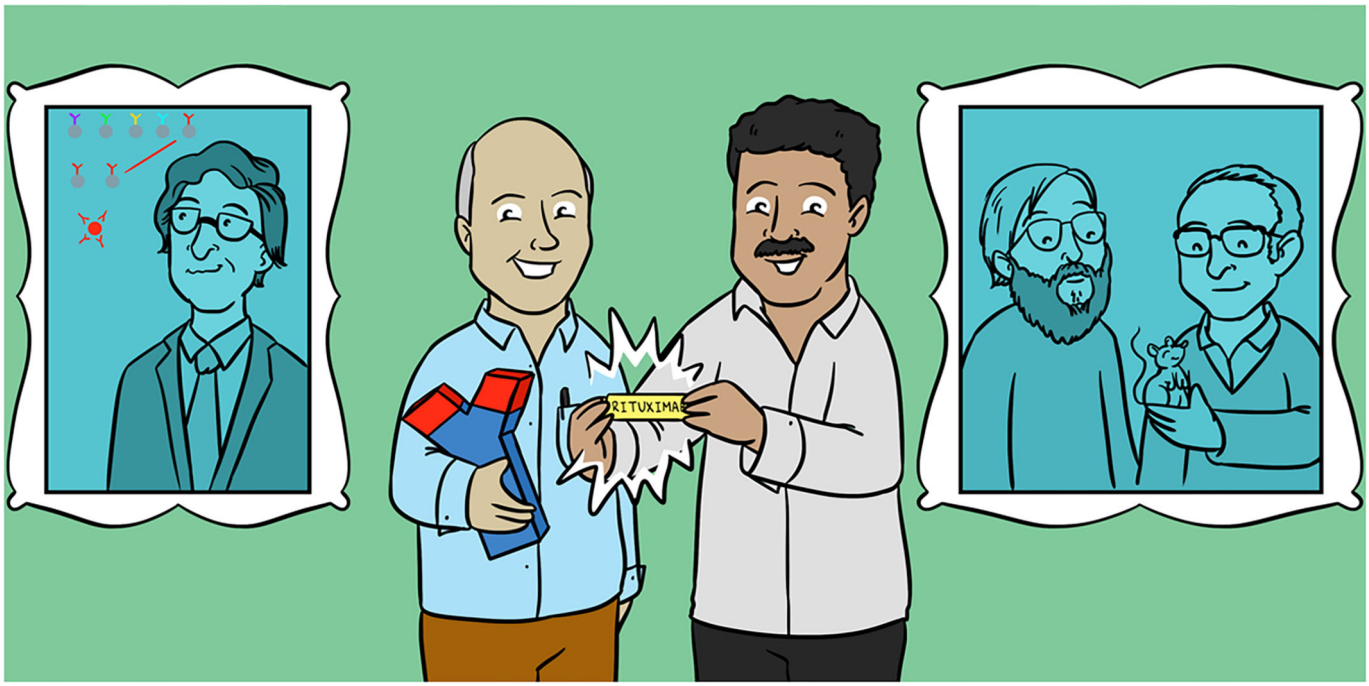

RITUXIMAB: A "MAGIC BULLET" FOR TREATING SOME BLOOD CANCERS

Robert Busch *

Department of Life Sciences, University of Roehampton, London, United Kingdom

YOUNG REVIEWERS:


JAKOBY
AGE: 11


JEREMY
AGE: 10


KIRUBEL
AGE: 10


SYLVIA
AGE: 10

B cells are small white blood cells that contribute to our immune defenses. They produce antibodies, which help us to recover from infections. B cells may cause diseases when they misbehave. If they mutate and then divide out of control, B cells can produce blood cancers called leukemias or tissue cancers called lymphomas. This article traces the development of Rituximab, a drug that kills cancerous B cells. Paradoxically, the drug is itself an antibody—the product of a B cell! Developing such an antibody into a drug required deep knowledge of the immune system, clever genetic engineering, and great effort by scientists and medical doctors. This is a story of several great scientists building on each other's work to create a drug that has saved many lives.

INTRODUCTION

This article tells the story of Rituximab, a drug used to treat cancers of the blood and lymph [1]. These cancers are caused by cells of the immune system that mutate and divide when they should not. Many

drugs used to treat such cancers work by killing *any* cell that divides, including cancer cells, which divide quickly. However, certain normal cells also need to divide all the time, including those lining the gut and the blood-forming cells in the bone marrow. These healthy cells are also killed by the anti-cancer drugs that target dividing cells. The harmful effects of these drugs limit their usefulness.

It would be better to kill *only* the cancer-causing cells, using a "magic bullet" (scientists use this expression to describe drugs that work very precisely on the cause of a disease, with minimal side effects). Rituximab is a drug that gets much closer to this ideal. Rituximab binds to a molecule called CD20, which is on the surface of certain immune cells, called B cells. Binding of Rituximab to B cells allows the removal of abnormal B cells that cause cancers. Rituximab also removes normal B cells, which are part of our immune defenses, but this is not very harmful: other immune cells can still protect us against most infections. Rituximab does not attack other cells in the body, because they do not have the CD20 molecule. Therefore, this treatment is less harmful and more effective than the older drugs.

The development of Rituximab involved many scientists building on each other's work over decades. They had to discover how B cells work within the immune system, how they cause disease, and how they can be distinguished from other cell types. They then had to use this knowledge to kill misbehaving B cells in human patients.

B CELLS IN DEFENSE AND DISEASE

We have all experienced feeling ill and tired, with sniffles, cough, or fever for a few days—and then we slowly start feeling better again. This misery can be caused by a common cold virus that enters our lungs and multiplies in our cells. The immune system fights the virus and restores our health. Without the immune response, we would quickly become a breeding ground for viruses and other infections.

ANTIGEN

The part of an infectious agent that stimulates B cells to make an antibody, and to which that antibody then binds.

ANTIBODY

A protein on B cells and in blood, which can bind to an antigen. Individual B cells each make a different antibody.

The immune system uses white blood cells and proteins in the bloodstream to find and kill infectious agents. Some white blood cells produce symptoms that help to fight infections: inflammation, tiredness, and fever. Other white blood cells and proteins fight infections in the body by identifying each infectious agent by the unique shapes of its molecules (called **antigens**). Recognition of antigens allows infectious agents to be attacked much more accurately.

B cells are a type of white blood cell that takes part in the immune response [2]. Each B cell has a protein on its surface called an **antibody**, which differs slightly from the antibodies on other B cells (Figure 1A). During an infection, B cells meet the infectious agent. If the infectious agent has an antigen to which a B cell's antibody binds, that B cell

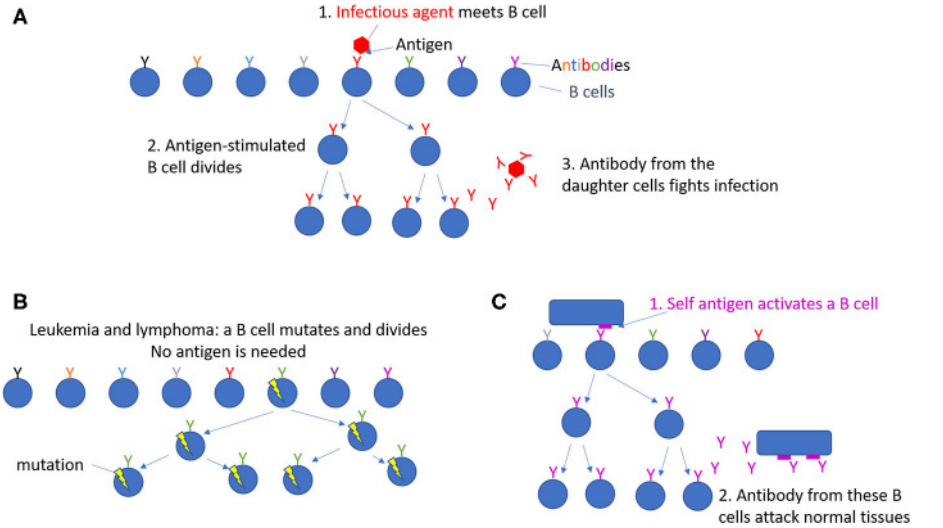

Figure 1

Division of B cells. **(A)** Each B cell has a unique antibody on its surface, shown here with various colors. Normal B cells only divide when an infectious agent enters the body. Then, the B cells specific for that infectious agent divide and make antibodies that fight this infection. **(B)** Leukemias and lymphomas can result from B cells that have mutated so they divide too much, even when no infection is present. **(C)** In autoimmune diseases, B cells divide and make antibodies that damage normal tissues.

will divide. This produces more B cells making the same antibody. Some of these cells will release their antibodies, so they can travel in the blood and bind to the infectious agent wherever it may be. The bound antibody targets the infectious agent for destruction by the immune system. Some of the responding B cells can survive for long periods, providing immune memory—a faster, more powerful response—when the same infectious agent enters the body again later in life. The scientist Niels Kaj Jerne discovered this explanation for immune responses [2, 3].

Most other B cells will not participate in this fight, because their antibodies cannot bind the same antigen. They may, however, respond to a different infection, another time. Humans have millions of distinct antibodies on their B cells. Only a tiny proportion of them becomes active in response to any one infection. Together, our B cells can fight any infections we may suffer.

At times, instead of fighting infections, B cells can *cause* diseases. Sometimes, mutations can occur in a B cell, causing it to start dividing all the time, even though no antigen is present to activate it (Figure 1B) [1]. The mutated B cells build up in the blood as a cancer called **leukemia**, or elsewhere in the body, forming a cell mass called a **lymphoma**. The cancerous B cells can disrupt the normal functions of the blood or organs where they build up, ultimately causing death. Many types of leukemia and lymphoma exist; only some come from misbehaving B cells[1] . In other patients, B cells make antibodies that attack normal, uninfected tissues in the body by mistake (Figure 1C). Diseases caused by such errors are called **autoimmune diseases** and can attack joints, blood vessels, the brain, or other tissues.

LEUKEMIA

A disease in which mutated immune cells build up in the blood.

LYMPHOMA

A disease in which mutated immune cells build up in solid tissues.

AUTOIMMUNE DISEASE

A disease in which the immune system attacks a normal part of the body.

[1] A different paper in this journal [4] describes another type of leukemia and the development of a very different "magic bullet" to treat it.

IDENTIFYING HUMAN B CELLS USING MICE

To develop a drug for treating blood cancers, scientists first had to learn how to distinguish human B cells (including the mutated B cells that form leukemias and lymphomas) from other types of white blood cells. So far, you have learned that antibodies are used by the immune system to recognize infectious organisms...but scientists have learnt how to produce antibodies that recognize specific cell types, like B cells, too! This way of using the immune system was first developed in mice.

In the 1970s, Georges Köhler and César Milstein, working in Cambridge, Britain, used mice to develop a process for creating antibodies against a specific antigen [3]. They started by immunizing a mouse with an antigen. The mouse made an immune response, in which some B cells divided and made antibodies that could bind the antigen. Next, they grew B cells from the mouse one by one in tiny culture dishes and forced them to divide all the time. They were then able to identify, among thousands of such cultures, those B cells that made antibodies specific for the immunizing antigen. Those B cells were grown in large numbers to obtain the unique antibody made by that first B cell and all the cells that grew from it, called daughter cells. A single cell together with all its daughter cells is called a clone, because all the cells make the exact same antibody. The antibody produced by a single clone of B cells is called a **monoclonal antibody**.

MONOCLONAL ANTIBODY

An antibody made by a single B cell and its daughter cells, which is produced in large amounts in the lab.

But how did this help scientists identify *human* B cells? In mice, monoclonal antibodies can be made against any antigen that is foreign to the mice. Since human B cells are foreign to mice, mice immunized with human white blood cells will make some antibodies specific for molecules present on human B cells (Figure 2). Using the method to make monoclonal antibodies described above, scientists identified a molecule called CD20, which was found on human B cells but not on other cells in the human body. When B cells are mutated and become cancerous, they continue to have CD20 on their surfaces. Antibodies that bind to CD20 can therefore be used to identify both normal and cancerous B cells [5].

TURNING CD20-SPECIFIC ANTIBODIES INTO A DRUG THAT WORKS IN HUMANS

We have seen that the immune system kills infectious agents to which an antibody has bound. Is it possible, therefore, to kill B-cell leukemias or lymphomas simply by injecting CD20 antibodies from mice into patients? Unfortunately, antibodies from mice do not work well with the other parts of the human immune system that are needed to kill antibody-coated infectious agents, so one more step was needed to create an effective drug [5].

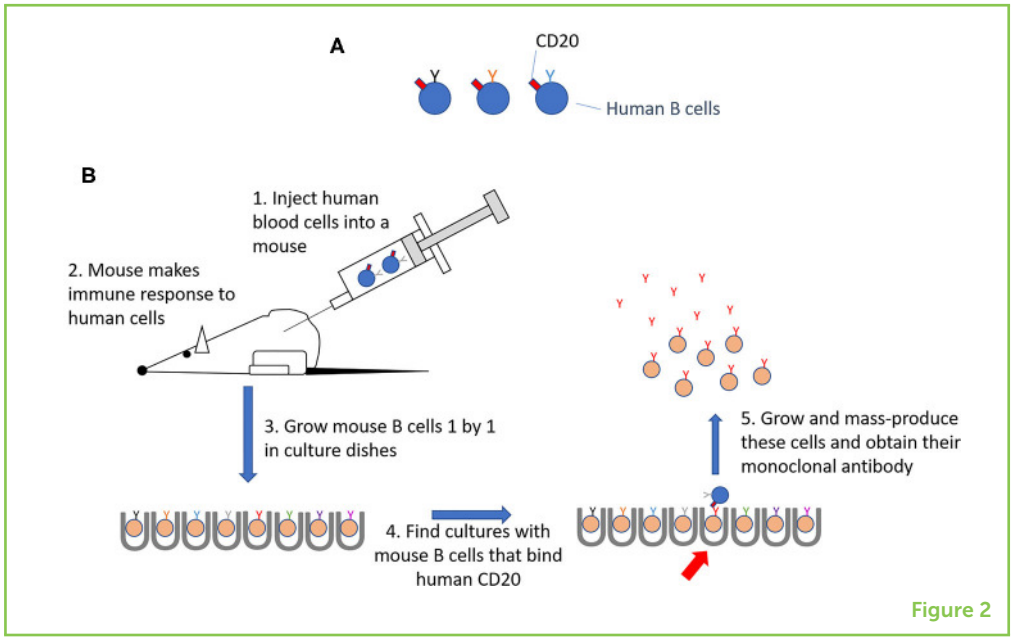

Figure 2

Making antibodies that identify human B cells. **(A)** CD20 is on all human B cells. **(B)** Human blood cells, including B cells, were injected into mice to stimulate an immune response. B cells from the immune mice were grown up one by one. One mouse B cell was found that made an antibody that bound to CD20 on human B cells. This clone was grown as a source of this antibody.

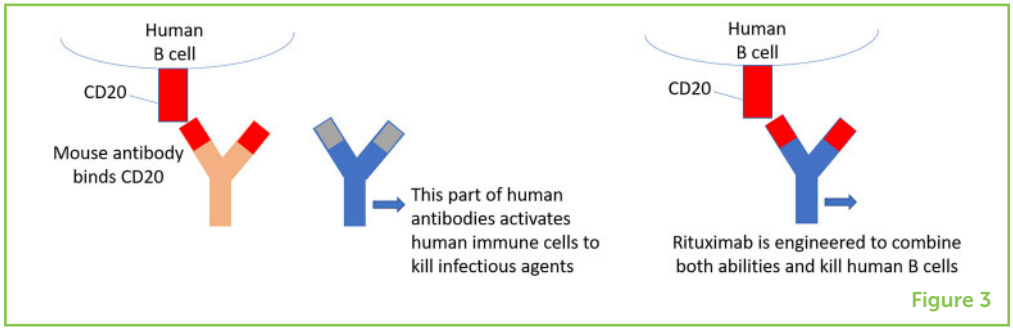

Figure 3

How Rituximab was made. Rituximab contains part of a monoclonal antibody from a mouse, which binds to human CD20, attached to the rest of an antibody molecule from a human, which can work within the human immune system to kill cells to which the antibody binds. This combination is not found in nature but can be created by genetic engineering.

GENETIC ENGINEERING

The laboratory process by which scientists modify DNA to create molecules or organisms with novel properties.

Antibodies are shaped like the letter "Y" and the different parts of the "Y" have different functions (Figure 3). The antigen binds to the two tips of the "Y," while the stem of the "Y" activates the immune system to kill. A laboratory process called **genetic engineering** can be used to create artificial molecules, by arranging genetic material in new combinations. A group of scientists at IDEC Pharmaceuticals Corporation, a biotechnology company in San Diego, United States, did this to create Rituximab [1, 5, 6]. Rituximab contains the tips of the "Y" from a mouse monoclonal antibody that binds to CD20. The remainder of Rituximab comes from a human antibody, which works well in the human immune system. This artificial antibody—part human, part mouse—proved to be an effective drug for killing B cells.

Rituximab passed safety tests in animals and was then given to patients with B-cell lymphomas. It was a great success, curing more people than a combination of drugs that kill dividing cells, and with fewer toxic side effects. Since 1997 when Rituximab was first given to lymphoma patients on a large scale, patient survival has greatly improved. Combining Rituximab with other drugs was even more effective. Later, benefits were shown in B-cell leukemias [1].

Nowadays, Rituximab is used to treat other diseases in which B cells cause harm without becoming cancerous [7]. We have seen that B cells sometimes cause autoimmune diseases by attacking a normal part of the human body by mistake. In some of these diseases, too, Rituximab, or similar antibodies, have been effective treatments.

CONCLUSIONS AND OUTLOOK

We have seen that a powerful new drug, Rituximab, was made by first identifying B cells of the human immune system using monoclonal antibodies. Genetic engineering helped to improve the effectiveness of those monoclonal antibodies at killing cancerous B cells in the human body. This story highlights how scientists and medical doctors can work together, over many years, to improve and prolong lives. Rituximab was one of the first monoclonal antibodies developed to treat human blood cancers. Monoclonal antibodies have become important products made by the biotechnology industry for the treatment of many diseases, as well as for diagnosing illnesses and for laboratory research. From the successes (and some failures) of Rituximab and other monoclonal antibodies in the treatment of patients, we continue to learn more about the diseases themselves. Maybe someday you will join us in this effort.

ACKNOWLEDGMENTS

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YOUNG REVIEWERS

JAKOBY, AGE: 11
Jakoby likes to play basketball with friends as well as read.

JEREMY, AGE: 10
Jeremy like to bake, play, sports, and listen to music. If he is not doing any of those things, he reads books about history, math, and science.

KIRUBEL, AGE: 10
Kirubel likes to read books, doing math, and learning by watching videos about animals. He also he likes to play soccer, basketball and watching movies.

SYLVIA, AGE: 10

Sylvia enjoys drawing and The Simpsons, and would like to learn more about health.

AUTHOR

ROBERT BUSCH

I work in the Department of Life Sciences at the University of Roehampton, in London, UK. I teach about molecules, cells, and diseases affecting the immune system. In my research, I study molecules called tissue antigens, which are an important reason why organ transplants are rejected by the immune system. I seek to understand how tissue antigens influence the development of autoimmune diseases. I have collaborated with medical doctors to study how a drug called Rituximab affects the immune system. I also study the effects of vitamin D on immune cells. In my spare time, I sing in choirs. *robert.busch@roehampton.ac.uk

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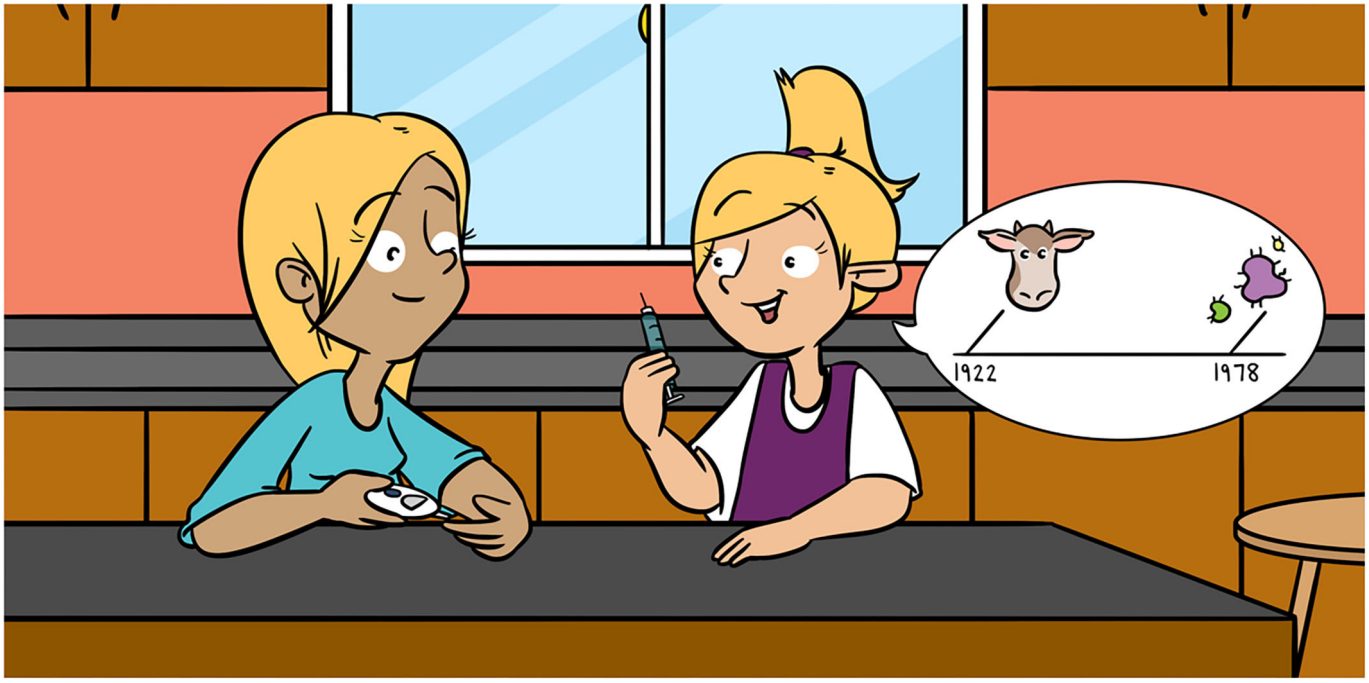

SUGAR, DOGS, COWS, AND INSULIN—THE STORY OF HOW DIABETES STOPPED BEING DEADLY

Astrid Christine Hauge-Evans *

Health Sciences Research Centre, Department of Life Sciences, University of Roehampton, London, United Kingdom

YOUNG REVIEWERS:

AMELIE
AGE: 12

SANTIAGO
AGE: 12

Before the discovery of insulin, diabetes was a life-threatening and untreatable illness. It was caused by very high blood sugar levels and many children died from it. In 1922, two scientists, Frederick Banting and Charles Best, treated a boy suffering from diabetes with special extracts from a cow's pancreas. The pancreas is an organ found near the stomach. The treatment lowered the boy's blood sugar to normal levels due to a chemical substance from the pancreas. This substance was later named insulin. In this article you will read about diabetes and insulin. You will see that the final discovery of insulin built on the work of many scientists before Banting and Best. It is a great story showing how the skills and determination of different people together led to a ground-breaking discovery. In 1978, human insulin was made artificially from bacteria and today it continues to save millions of lives.

WHAT IS DIABETES?

DIABETES

A condition in which glucose levels in the blood become dangerously high. In type 1 diabetes, insulin is not produced by the pancreas. In type 2 diabetes, the body does not respond to insulin and the pancreas does not make enough insulin.

INSULIN

A chemical substance made by cells in the islets of Langerhans. The main role of insulin is to help the body to use glucose as a source of energy.

A high level of sugar in the blood can be dangerous and is the main sign of an illness called **diabetes**. Before **insulin** was discovered, many people died from this illness. Diabetes has been known for a long time. The Egyptians wrote about it in medical scrolls more than 3,500 years ago in the Ebers Papyrus [1], and there are records of treatments for diabetes dating back to ancient India and China [2].

Aretaeus of Cappadocia, a Greek doctor in the 2nd century AD, first used the word "diabetes," which means "siphon" or "pass through." This word was chosen because people with untreated diabetes needed to urinate a lot, as if water flowed through their bodies. Other old medical writers described how the body wasted away and suggested that "waste" was lost in the urine. This fits with another sign of the illness, weight loss. Other symptoms include thirst, hunger, and tiredness.

The full medical name of diabetes is diabetes mellitus. Mellitus means "sweetened with honey" and was chosen because of the presence of sugar in the urine, which is caused by high levels of sugar in the blood. The sweetened urine attracts insects. Nowadays we can measure blood sugar levels directly, but before that was possible, diabetes was sometimes detected by testing whether or not ants were attracted to the sweetness of the urine.

GLUCOSE

Carbohydrate from the diet is made up of smaller units. Glucose is the most common and important of these units as it is the main source of energy fuel for the body.

KETOACIDOSIS

A condition in which the blood becomes acidic due to the production of high levels of ketone bodies. When glucose is not available, the liver makes ketone bodies from fat molecules to provide energy for the brain.

The problem with diabetes is that, although there is plenty of sugar in the blood, the body cannot use it and instead eliminates it in the urine. **Glucose** is the most common type of sugar in the body and it is the main source of energy for the body's cells, including the brain cells. When someone has diabetes, the cells cannot get access to glucose and starve instead. To solve this problem, the body makes energy from fat instead of glucose. A side effect of this process is that the blood becomes very acidic. This is called **ketoacidosis** and it can cause a person to go into a coma or even die. It is therefore extremely important to help the cells use glucose and to lower blood glucose levels.

DIFFERENT TYPES OF DIABETES

There are at two main types of diabetes, type 1 and 2, and both are linked to a substance called insulin. Insulin is a chemical that is normally made by the body and it controls blood glucose levels, mainly by signaling to cells that they need to take up glucose from the blood. In type 1 diabetes, people cannot make insulin. In type 2 diabetes, insulin is at first being made, but the cells cannot respond to it properly. This is referred to as **insulin resistance**. In both cases, glucose is not moved into the cells. With time, people who develop type 2 diabetes also become less good at making insulin.

Figure 1

The pancreas is located next to the stomach, liver, and small intestine. In this image the stomach is not shown, so you can see the pancreas. The duodenum, which is the top part of the small intestine, is connected to the stomach (figure modified from Freepik.com resource).

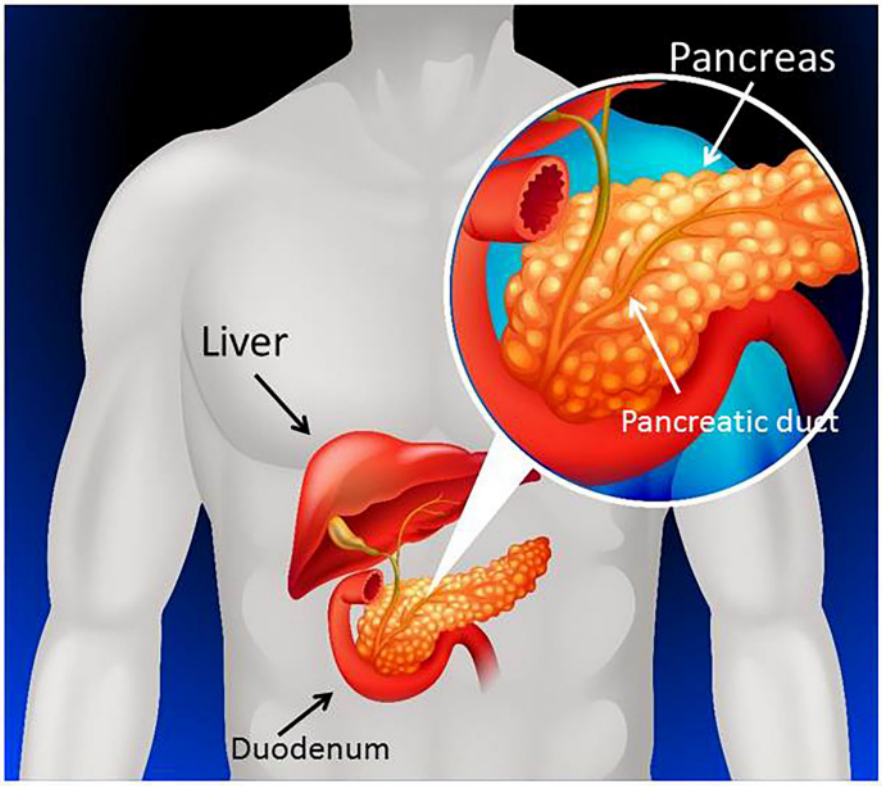

Figure 1

WHAT CAUSES HIGH LEVELS OF GLUCOSE IN THE BLOOD?

INSULIN RESISTANCE

A condition in which cells do not detect or respond to insulin. Insulin-resistant cells fail to take up glucose from the blood and thus cannot use glucose for their energy needs.

PANCREAS

An organ which helps the conversion of food to energy in the body by producing chemical messengers (hormones), such as insulin. It also makes digestive enzymes, which help break down food in the small intestine.

Our bodies get energy from the foods we eat. The main parts of food are fats, carbohydrates, and proteins. Carbohydrates are an essential energy source and are found in foods, such as bread, rice, and pasta but also in fruit, vegetables, and dairy products. Carbohydrates are broken down in the stomach and intestine into smaller units, including glucose. In the small intestine, glucose is transferred into the blood stream. Therefore, glucose levels in the blood increase after a meal. Normally, the blood will transport the glucose to cells all over the body, where it is taken up with the help of insulin and used as a source of energy.

Some famous experiments in 1890 by two German doctors, Oskar Minowski and Joseph von Mering, showed that an organ next to the stomach and the liver called the **pancreas** (Figure 1) is also essential for controlling blood glucose levels. If the pancreas was removed in dogs, the animals would very rapidly develop serious signs of diabetes [3].

Figure 2

The islets of Langerhans are small clusters of cells scattered throughout the pancreas, shown here as small groups of blue dots. The square in the lower right shows a section of a real pancreas under a microscope, where you can see an islet surrounded by non-islet pancreas. Beta cells make insulin and alpha cells make another pancreatic hormone, glucagon. Insulin and glucagon are released into the blood stream via a type of blood vessel, the splenic artery (pale purple arrows). Release of digestive enzymes into the small intestine is shown with orange arrows (see glossary) (from: Wikimedia Commons: The pancreas).

ISLETS OF LANGERHANS

Groups of cells located in the pancreas. They are responsible for the production of insulin and other hormones from the pancreas.

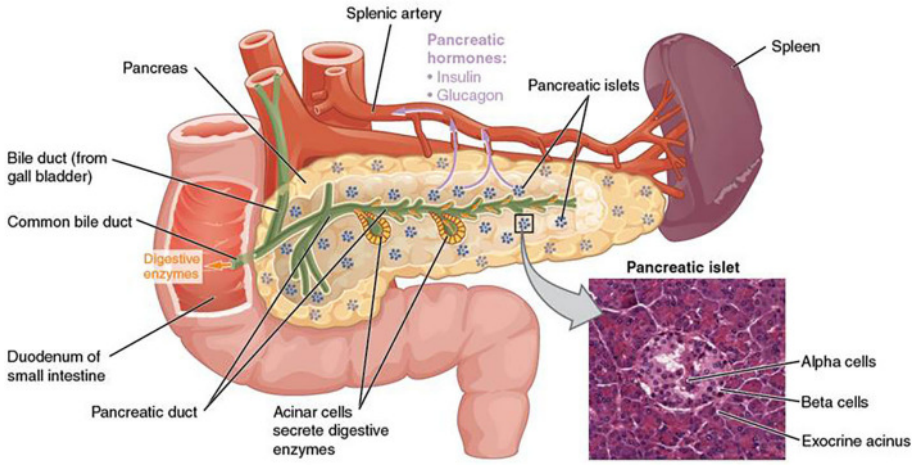

Figure 2

WHAT IS SPECIAL ABOUT THE PANCREAS?

In 1869, a medical student named Paul Langerhans was studying a rabbit pancreas under the microscope. He saw something interesting—not all pancreatic cells were the same. There were clusters of similar-looking cells dotted throughout the pancreas like small islands in the sea. Langerhans did not know why the cells were arranged this way or whether they were different from the rest of the pancreas. In 1893, these small mini-organs were named **islets of Langerhans** by another scientist, Edouard Laguesse, who saw the same pattern in the human pancreas. We now know that there are about one million of these islets in a human pancreas (Figure 2). Laguesse suggested that these islets could make a chemical that might regulate blood glucose levels, but at that time it was just an idea.

Other observations helped scientists develop this idea further. The pancreas is connected to the small intestine via a tube called the pancreatic duct. If this tube was blocked experimentally, all the non-islet cells eventually died. However, the islets kept their normal structure for much longer, which confirmed that islets really were different from the rest of the pancreas.

Scientists also noticed that urine glucose levels did not increase in animals that had their pancreatic ducts blocked, because their islets were still working. In contrast, glucose levels were high in animals that had the whole pancreas removed. These types of experiments were carried out by many different scientists from Italy, Germany, France and the UK around the turn of the 19th century [3]. They suggested that only the islets, and not the rest of the pancreas, control blood glucose. It was later discovered that the islets control blood glucose levels through the production of insulin.

INSULIN PRODUCED BY THE ISLETS OF LANGERHANS CONTROLS GLUCOSE LEVELS

But how would it be possible to get hold of insulin to treat people with diabetes? Two scientists, with the help of their co-workers, have become famous for doing just that. Frederick Banting was from Canada and worked as a medical officer during the First World War, where he was injured. Once home again, he read about the experiments other scientists had done and decided to isolate islets from the pancreas and extract the insulin from them. He started working in the laboratories of a professor in Toronto, John MacLeod, together with a research assistant, Charles Best. They carried out experiments with dogs in which the pancreatic ducts were blocked, just as Banting had read about. Since the non-islet pancreas broke down during this treatment, they were able to isolate the islets.

Getting the insulin out of the islets was more difficult, and they had to repeat their experiments many times to get the insulin pure enough. Together with another team member, James Collip, they were eventually able to remove unwanted chemicals and concentrate the insulin from the pancreas. Banting also learned that they could use pancreas extract from cows rather than dogs. This was an important finding, because the cow pancreases were available from animals already killed for food, and much more insulin could be extracted. Excitingly, the scientists found that the purified insulin reduced blood glucose levels when it was injected into diabetic animals and then they were ready to test the extract in humans [4].

Banting and Best worked across the road from a hospital where a 14-year-old boy named Leonard Thompson was a patient, suffering from diabetes. On 11th January 1922, Thompson was injected with the insulin made by Collip, Best, and Banting, but unfortunately it did not work. Collip then made an even purer extract, which was used on 23 January 1922—this time it worked! Leonard's blood glucose levels went down, his blood became less acidic, and he felt a lot better [5]. The same happened when six other people on the ward received the treatment.

This was the turning point—it meant that diabetes was no longer deadly. But there was still work to do. Large amounts of insulin were needed, so scientists developed methods of scaling up its production. They also discovered the genetic code for human insulin and set up clever experiments in which that code was inserted into bacteria that would then make large amounts of human insulin. In 1978, human insulin was made from bacteria for the first time and it continues to save millions of lives today.

ONE DISCOVERY—MANY SCIENTISTS

Banting and MacLeod received the Nobel Prize in 1923, but the discovery of insulin was due to the work of many scientists. It started with medical observations in the ancient world and went on to involve people from countries across Europe and America. Scientists throughout the world still carry out diabetes research. Some scientists work on improving diabetes treatment and others investigate why islets stop making insulin in the first place. Some study whether certain cells can be changed to become like islets, so that they will make insulin. But the ultimate aim is to one day find a way to prevent or even cure diabetes, which will improve and save the lives of millions of people around the world.

ACKNOWLEDGMENTS

Figure 1 has been designed using a resource from Freepik.com and Figure 2 is modified from the free image depository Wikimedia Commons (File 1820: The Pancreas; OpenStax College/CC BY (https://creativecommons.org/licenses/by/3.0).

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YOUNG REVIEWERS

AMELIE, AGE: 12
I have been participating in Frontiers for Young Minds for the past 2 years. Reviewing papers is one of my passions as well as reading, painting, drawing, and writing. Through reading these scientific papers, I have learnt a lot about health and disease. I love to travel and my favorite animal is the pangolin.

SANTIAGO, AGE: 12
Hello my name is Santiago and I am 12 years old, you can call me Santi. My favorite sport is soccer. I play for a team and my position is defending midfield. I like to play with my friends. I am in the sixth grade. I like History, Science, and especially chemistry or lab experiments.

AUTHOR

ASTRID CHRISTINE HAUGE-EVANS
I am a scientist in the Department of Life Sciences at University of Roehampton in London, UK, where I teach Nutrition and Health. I am interested in how the pancreatic islets make insulin and how this process sometimes fails in diabetes. There are many factors both inside and outside the body which affect this process. They include signals from the brain, the stomach and gut, as well as signals from cells within the islets. I am interested in how the cells in the islets talk to each other and change the production of insulin. I am also studying how other things in our diets, such as coffee and whole grains, can improve or worsen how well the islets make insulin. *Astrid.Hauge-Evans@roehampton.ac.uk

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HEALTH
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ALBERT SZENT-GYÖRGYI—THE SCIENTIST WHO DISCOVERED VITAMIN C

Hana Shiref and Michelle A. Sahai **

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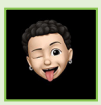
YOUNG REVIEWERS:


ALESSIO
AGE: 15


ANTONIO
AGE: 14


DAVIDE
AGE: 15


GIOVANNI
AGE: 14

In the 1920s and 1930s, Dr. Albert Szent-Györgyi, a Hungarian professor of medicinal chemistry, made some very important discoveries that help us to understand basic nutrition. While conducting a series of early experiments on citrus plants, he found that plant browning could be caused by peroxidase, a plant enzyme that is active during oxidation. By adding citrus juice to peroxidase, the browning process could be stopped. In his experiments he isolated a substance he called, hexuronic acid that he thought was active within citrus juice. This was one of the first steps in the discovery of what we know today as vitamin C. Szent-Györgyi, also conducted experiments on guinea pigs, which are similar to humans, in that they have to consume hexuronic acid to remain healthy. He decided to rename hexuronic acid to ascorbic acid or vitamin C, reflecting its anti-scorbutic (scurvy fighting) properties. It took many years to find a way to produce large amounts of ascorbic acid from natural sources. It was by chance he found the answer in his dinner! The story goes that he did not want to eat the paprika in his dinner, so he took it to his laboratory, where he found it to contain large

amounts of vitamin C. Without his discovery we would not know that vitamin C is important for proper functioning of our immune system. By eating our daily dose of fruits and vegetables, which contain vitamin C, we improve the repair and growth of tissue and many more factors that keep us healthy. Szent-Györgyi was awarded the Nobel Prize in Physiology or Medicine in 1937 for his discovery of vitamin C. He is also known for his later contribution to what we know as the Citric Acid (Krebs) cycle.

> **"Discovery consists of seeing what everybody has seen and thinking what nobody has thought."**
>
> *-Albert Szent-Györgyi in Irving Good, The Scientist Speculates (1962).*

Vitamin C's discovery begins with a disease called **scurvy**. Prolonged vitamin C deficiency leads to scurvy and, if left untreated, can be fatal. Symptoms of scurvy include feeling tired, bleeding gums or skin that bruises. As these symptoms worsen, patients may develop open sores, lose teeth and can even die. Other symptoms include impaired wound healing, muscle weakness and hemorrhages (an escape of blood from a ruptured blood vessel). Sounds pretty nasty, right? People have complained about this disease since ancient times. Some records of scurvy have been around since 1500 BC Egypt [1]. Scurvy was a big problem for sailors in the eighteenth century. They ate a lot of dried meats and grains and did not include fruits and vegetables in their diet. This was because these foods would not remain fresh on long sea journeys. In 1757, James Lind, a Scottish doctor, discovered that fresh citrus fruits could prevent scurvy. It was then mandatory for sailors in the British navy to consume citrus fruits and lemon juice [2].

In 1907, other scientists like Axel Holst and Alfred Frohlich proposed that a special substance existed in these fruits [2] while Casimir Funk coined the term Vitamin C in 1912 [3]. He developed the concept of **vitamins**, and showed that these "vital" substances were needed to keep people healthy and free of disease. His terminology as well as the discovery made by Holst and Frohlich led to the substance being called "water-soluble C" which then eventually became Vitamin C. Only in 1928 did the scientist Albert Szent-Györgyi identify this unique substance, which he referred to as **hexuronic acid** [2].

WHAT IS VITAMIN C?

Ascorbic acid (vitamin C) is an organic compound made of carbon, hydrogen, and oxygen (Figure 1). It is a white solid, made synthetically from sugar dextrose when it is in its purest form. It can also be used as a vitamin supplement or as a food preservative [4].

VITAMIN C

A water-soluble vitamin important for healthy skin, teeth, bones, and blood vessels. It is found especially in citrus fruits, tomatoes, potatoes, and green leafy vegetables. Also called ascorbic acid.

SCURVY

A disease caused by a lack of vitamin C, characterized by anaemia, spongy gums, bleeding beneath the skin, and (in infants) malformation of bones and teeth.

VITAMIN

Vitamins are a group of organic micronutrients that are required by the body for healthy growth, development and immune system functioning.

HEXURONIC ACID

Any uronic acid derived from a hexose. Was also known as Ascorbic acid (vitamin C).

ASCORBIC ACID

See Vitamin C.

Figure 1

Ascorbic acid or Vitamin C. The **(A)** 2-dimensional structural formula and **(B)** 3-dimensional structure of ascorbic acid. The black, red, and white colors represent the atomic elements carbon, oxygen, and hydrogen, respectively.

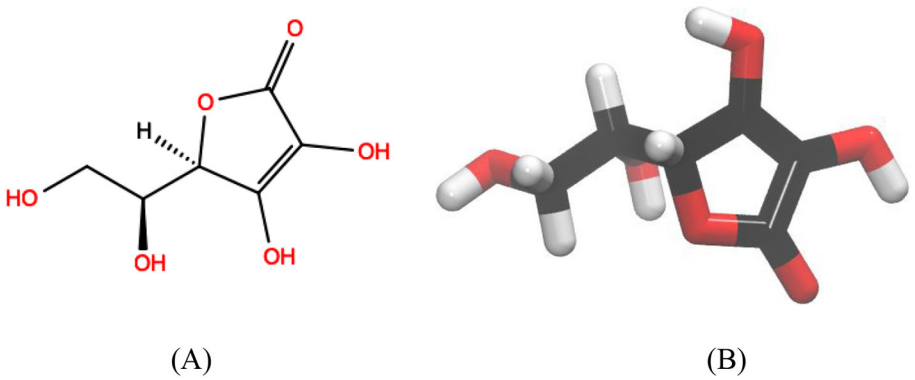


Figure 1

WHY IS VITAMIN C SO IMPORTANT?

Have your parents told you to drink orange juice when you were sick? This is because orange juice has a high level of vitamin C and can keep us healthy or treat a cold. The human body is unable to produce vitamin C and we must therefore get it through our food or by taking a **multivitamin**.

MULTIVITAMIN

A pill or tablet containing several vitamins.

Vitamin C allows the body to use carbohydrates, fats, and protein. It acts as an antioxidant, meaning it can chemically bind and neutralize the tissue damaging effects of substances called free radicals. It is important for the growth and health of bones, teeth, blood vessels, gums, and ligaments. It is also involved in the forming of collagen, the main structural protein within the body. Collagen is vital for the proper functioning of internal organs [4].

FOOD SOURCES WITH VITAMIN C

Did you know that many fruits and vegetables can provide you with the correct amount of vitamin C? They include foods like oranges, lemons, spinach, kiwifruit, strawberries, limes, tomatoes, grapefruit, Brussels sprouts, red and green peppers, cabbage, potatoes, and broccoli. Cooking your food can destroy vitamin C, so it is good news that there are many food sources of vitamin C to keep you healthy! [4].

EARLY LIFE AND THE DISCOVERY OF HEXURONIC ACID

Albert Szent-Györgyi was born on 16 September 1893 in Budapest, Hungary. His family had produced three generations of scientists [2]. As a result, he developed an interest in science from an early age. He studied medicine at the University of Budapest and also worked in his uncle's laboratory before World War I. He served in the military during the war and in 1917 had to leave the military after being injured. He also received a Silver Medal of Military Valor for his service. After receiving his medical degree, he went on to study at different European universities [2].

His scientific career began with studying the chemical changes that happen when cells in our body use proteins, fats, and carbohydrates. This process is called cellular respiration. He studied this process by isolating a molecule in the adrenal glands, which are small glands located on top of each kidney that produce a variety of hormones. This molecule is able to lose and regain hydrogen atoms and contains six carbon atoms. It also contains properties of both sugar and an acid. Albert Szent-Györgyi named it hexuronic acid because of these properties.

In the 1920's, Szent-Györgyi's interest turned to cellular respiration and energy production in plants. He started to investigate the browning processes that interrupt growth and normal functioning. He found that plants begin to brown because of cellular damage. This damage affects the mechanism that supplies hydrogen, which stops oxidation—a process in which one atom strips electrons from another, claiming them as its own. He found that browning could be caused by peroxidase, a plant enzyme that is active during oxidation. By adding citrus juice to peroxidase, the browning process could be stopped. In his experiments he isolated the hexuronic acid substance that he thought was active within citrus juice.

He started to work with a chemist named J. L. Svirbely. Svirbely and Szent-Györgyi conducted experiments on guinea pigs. Guinea pigs are similar to humans, because they have to consume vitamin C to remain healthy. This is because it cannot be made within their bodies.

In this experiment, the animals were divided into two groups. One group of guinea pigs received boiled food, where the boiling process destroyed vitamin C. The other group was fed food that was enriched with hexuronic acid. The second group thrived and remained healthy, whilst the first group developed scurvy-like symptoms and later died. Szent-Györgyi and Svirbely decided to rename hexuronic acid to ascorbic acid, reflecting its anti-scorbutic (scurvy fighting) properties [4]. By 1933, Szent-Györgyi had used all of the hexuronic acid he isolated from the adrenal glands of the guinea pigs. He then had to find natural sources of vitamin C to complete his study.

VITAMIN C IN PAPRIKA!

Orange juice and lemon juice contain high levels of ascorbic acid. They also contain many sugars which makes it difficult to obtain a pure sample. Szent-Györgyi therefore thought of a surprising solution—using paprika. Paprika is native to Szeged, Hungary. Szent-Györgyi wrote in his autobiography that one night after his wife served fresh red paprika for dinner: "I did not feel like eating it, so I thought of a way out. Suddenly it occurred to me that this is the one plant I had never tested. I took it to the laboratory… [and by] about midnight I knew that it was a treasure chest full of vitamin C." In his

laboratory he used paprika to produce 3 lbs of pure crystalline ascorbic acid. This was enough to give to the vitamin C-deficient guinea pigs and he determined that this acid was equivalent to vitamin C [5].

NOBLE PRIZE WINNING WORK: THE CITRIC ACID (KREBS) CYCLE

Do you remember Albert Szent-Györgyi's earlier work on plant respiration? He studied cellular respiration processes within muscle cells and conducted experiments on the pectoral muscles of pigeons. He looked at the processes in this biochemical cycle that produce energy in the form of adenosine triphosphate (ATP) from proteins, carbohydrates, and fats. ATP is known to be the source of energy within cells. He noticed that ATP had a very important role. He also identified the role of fumaric acid in this process. In 1937, Szent-Györgyi was awarded the Nobel Prize in Physiology or Medicine to for these discoveries.

CITRIC ACID CYCLE

Also known as the Krebs Cycle; a metabolic pathway found in aerobic organisms that oxidizes acetyl coA groups to carbon dioxide and water, producing 1 ATP, and a number of coenzymes that play a vital role in the next step of respiration, oxidative phosphorylation.

Another scientist, Hans Krebs, found that citrate (or **citric acid** in its protonated form), the first molecule to form during the cycle's reactions, was very important. This cycle is known as the Citric Acid (Krebs) Cycle, referring to both Szent-Györgyi's and Krebs' work (Figure 2). It is also called the tricarboxylic acid cycle due to the three-carboxyl groups found on its first two intermediates.

This cycle contains eight steps that take place within the matrix of the mitochondria of the cell and is central to cellular respiration. The four-carbon molecule, oxaloacetate, which begins the cycle is regenerated after the eight steps (Figure 2). These steps are a series of redox, dehydration, hydration, and decarboxylation reactions. One turn of the cycle releases two carbon dioxide molecules and produces three NADH, one FADH2, and one ATP/GTP. These molecules will then be utilized in further steps of cellular respiration, producing ATP for the cell [6].

LATER WORK AND LEGACY

In 1947, after receiving the Nobel prize, Albert Szent-Györgyi immigrated to the United States. He worked at the Institute for Muscle Research in Woods Hole, Massachusetts. He continued to research and investigate the causes of cell division and cancer. Albert Szent-Györgyi died on 22 October 1986. No doubt we owe much to this great scientist, whose landmark discoveries laid the foundation for proper nutrition.

Figure 2

Overview of the citric acid (Krebs) cycle that consists of eight steps. Created with BioRender.com.

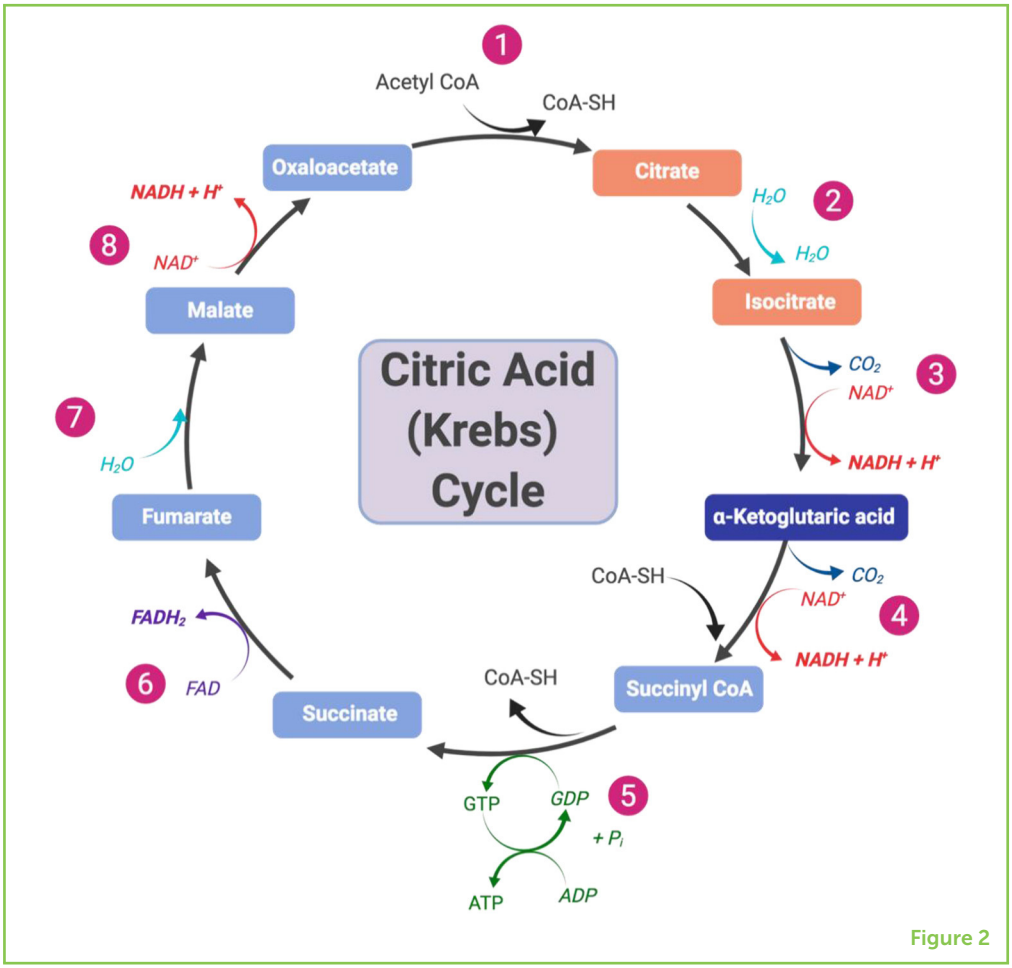


Figure 2

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YOUNG REVIEWERS

ALESSIO, AGE: 15
I am a High School student. I live in Naples and I like playing videogames and watching anime. My favorite sport is football.

ANTONIO, AGE: 14
Hi, my name is Antonio, I study electronic and I enjoy football and music.

DAVIDE, AGE: 15
Hi, my name is Davide. I am a student in electronic from Naples, I like all kind of sports and TV series and I really like foreign languages, especially English.

GIOVANNI, AGE: 14
My name is Giovanni, I am 14 years old and I attend a Neapolitan high school. I play guitar and I love metal.

AUTHORS

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HEALTH
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BEHIND A GREAT DRUG THERE IS A GREAT SCIENTIST: THE DISCOVERY OF A TREATMENT FOR PARKINSON'S DISEASE

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YOUNG REVIEWERS:

CORRADINO DI SVEVIA

AGES: 12–13

Parkinson's disease (PD) is a disorder of the brain that affects body movement. People with PD move slowly, have rigid muscles, and experience tremor (shaking). PD affects people's life quality and makes them disabled as the disease develops. Although PD was first described in the early nineteenth century, it remained untreated until some 150 years later. In the 1960s, an Austrian scientist, Dr. Oleh Hornykiewicz, discovered what happens to the brain in PD and showed that brains of deceased PD patients had very little of a chemical called dopamine in the area of the brain that is involved in movement control. He developed a treatment to replace the failing dopamine with its "parent" chemical, L-dopa. L-dopa reduces the symptoms of PD and is still used as a treatment for PD today. It has transformed the lives of millions of people with PD, helping their families and their carers.

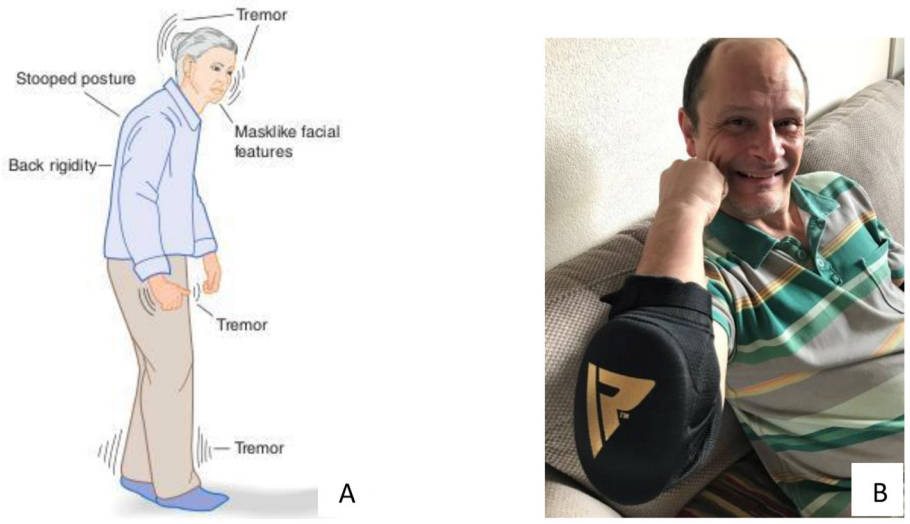

Figure 1

(A) Symptoms of PD include body tremor, stooped posture, and muscle rigidity (from slides_google.com). **(B)** A photo of a younger PD sufferer, Matt Eagles, who has lived with PD since his childhood, here wearing elbow pads to cushion the impact of falls (with permission of Matt Eagles).

INTRODUCTION

Body movement is a basic ability that we take for granted until it goes out of control. Such a loss of control happens in movement disorders, where the body is not properly balanced, not working in harmony, is jerky or slow to move, shaking or rigid. One of the most common movement disorders is **Parkinson's disease** (PD), which affects mainly the elderly but can also develop in younger people, both men and women.

PARKINSON'S DISEASE

A brain disorder characterized by slowed body movement, shaking and poor balance, caused by neurodegeneration or death of dopamine nerve cells.

AKINESIA

Loss of ability to move your muscles voluntarily.

The disease was first described by the English doctor James Parkinson in 1817. He called it "shaking palsy" because one of its symptoms is tremor, which means shaking of a body part, like the hands, when at rest. Other features of PD are the inability of people to move their muscles as they want to (this is called **akinesia**) and poor balance. People with PD move slowly, often with a stooped posture, and fall over very easily (Figure 1). The disease gets worse with time and patients with advanced PD become wheelchair bound and fully dependent on others.

PD affects over six million people across the world and hugely reduces their life quality. In addition, people with PD are likely to die early as a result of this disease. So, PD is a big problem for patients, their carers, doctors, and health services worldwide.

When Dr. Parkinson first described this disease, he knew its symptoms but not its cause. A disease with an unknown cause cannot be treated, and having no treatment is bad news for millions of PD sufferers. Scientific research is important and needed, because research can explain what goes wrong with the body when it is affected by a disease like PD.

In the case of PD, research has shown that there is a change in the way the brain works, so we say PD is a neurological disorder. Research on PD started about 70 years ago, and now we know a lot more about it. The earliest research was conducted by Dr. Oleh Hornykiewicz, who not only figured out what is going wrong with the brain in PD, but also discovered how to treat the slow movement and tremor symptoms of this disease. Dr. Hornykiewicz celebrated his 90th birthday in November 2016 and he still enjoys recognition for his life-long work, which has transformed the lives of PD patients, helped their families and carers. But it was not all easy at the beginning. Here is the story.

DR. OLEH HORNYKIEWICZ: THE BEGINNING

Oleh Hornykiewicz [1] was born on November 17, 1926, in a village near the city of Lvov, then in Poland and now in Ukraine. He spent his school years in Lvov and he fondly remembers his teachers. The outbreak of WWII in September 1939 badly affected his family. They were saved by Oleh's mother having Austrian roots, which gave them the right to move to Vienna, the capital of Austria. All their possessions had to be left behind and were never recovered. During the war, Oleh's brother was killed and his family suffered many hardships.

Despite the uncertainty and poverty of the post-war time, Oleh studied medicine at the University of Vienna and graduated in 1951. He then joined the Pharmacological Institute at the University of Vienna. Pharmacology is the study of how drugs work. Dr. Hornykiewicz worked very hard during this period, from early morning to mid-afternoon as an intern in the Rudolf's Hospital, and then from mid-afternoon to late night in Pharmacology, as an unpaid research assistant.

While in Vienna, Dr. Hornykiewicz saw some patients with neurological diseases, which later became useful in his research on PD. He came to England to work in the Department of Pharmacology at Oxford University with Professor Blaschko, who drew his attention to a recently discovered chemical substance called **dopamine**. Although they did not know the function of dopamine in the body, they knew it came from a "parent" chemical called **L-dopa** (Figure 2). The results of their work on these two chemicals convinced them that dopamine had an important role in the body. Further research showed dopamine to be a **neurotransmitter**, a chemical that helps with communication between the **nerve cells** that make up the brain.

In the meantime, another lab in England reported for the first time that dopamine is present in the brain of various animal species, including humans. Other researchers showed that L-dopa, the "parent" of dopamine, could increase the amount of dopamine

DOPAMINE

A neurotransmitter involved in the control of body movement, motivation, learning, pleasure, and other functions.

L-DOPA

A chemical that gets converted to dopamine in the brain. L-dopa can be used as a medical therapy to increase dopamine levels in Parkinson's disease.

NEUROTRANSMITTER

A chemical that acts as a messenger between nerve cells. Several dozen neurotransmitters have been identified in the brain so far, each with specific, often complex roles in brain function and behavior. Dopamine is one of them.

NERVE CELL

The basic unit of the brain also called "neuron." It is responsible for the communication within the brain by means of neurotransmitters.

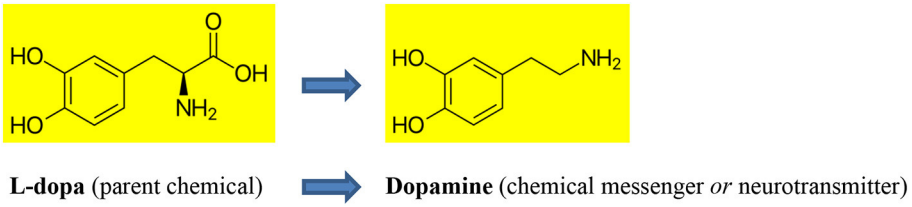

Figure 2

Dopamine is formed from its "parent" chemical, called L-dopa. Dopamine is a chemical that plays important roles in the body and brain. In the brain, dopamine acts as a messenger (called a neurotransmitter) that helps with communication between nerve cells. Dopamine is involved in movement control, perception of pleasure, reward-motivated behavior, and addiction to drugs.

in the brains of experimental animals that had low levels of this neurotransmitter [2].

This exciting result convinced Hornykiewicz that he needed to study the role of dopamine in the human brain after his return to Vienna in February 1958. His research question was: "What is the role of dopamine in brain function?" It helped him that another research group had just found that dopamine was present at high concentrations in the striatum region of the brain [2]. What is the striatum? As Figure 3 illustrates, it is part of the brain located deep under the brain's surface.

The striatum was known to be involved in the control of movement. Dr. Hornykiewicz connected the dots from much of the previous research on dopamine and the brain, and realized that dopamine was linked to the function of the striatum, which probably meant dopamine was involved in the control of body movement. This was a big step forward. At this point, Dr. Hornykiewicz knew that he wanted to do research on the role of dopamine in the human brain. I should say here that studies on chemical composition of tissue from freshly collected human brains had been rare at that time, so Dr. Hornykiewicz was pioneering a new approach, which has then been adopted by others, and fresh human brain material has become widely accepted as a source of information about human brain diseases. There are even brain banks that store human brains generously donated to scientific research.

THE DISCOVERY AND ITS MEANING: DOPAMINE IS DECREASED IN THE BRAINS OF PATIENTS WITH PD

In April 1959, Dr. Hornykiewicz and his team received the first brain of a patient with PD who had died. They collected the striatum region from the PD patient's brain, and also obtained striatum samples from a brain not affected by any known neurological disorder. They mashed up the tissues and treated the samples with acid to pull out chemicals, such as dopamine. We call it "extraction." They then conducted an experiment involving a color reaction to measure dopamine. In this experiment, the more dopamine present in the samples, the more pink the samples would be. I should mention that the method was

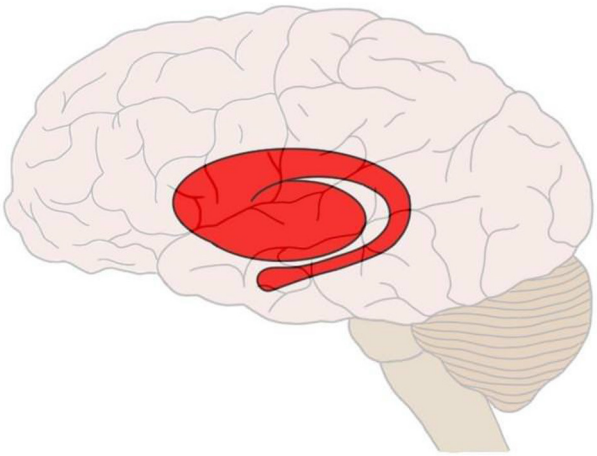

Figure 3

Figure 3

The striatum in the human brain, shown in red. The striatum is involved in the control of body movement apart from some other functions. It needs dopamine for the regulation of voluntary movement, and dopamine is released there from nerve cells that live outside the striatum. Graph from: https://www.neuroscientificallychallenged.com/.

much simpler than what we use today but it proves that when doing research, thinking comes before technology, and that complicated equipment is not essential to discover something important. So what did they discover? While the samples from the normal brain were pink, indicating the presence of dopamine, the PD samples showed only a faint touch of pink color. So, Dr. Hornykiewicz discovered that there was much less dopamine in the brain of the PD patient, and that the area affected was the striatum, which controls body movement. This was a big discovery, but they needed more brain samples to make sure their findings were true [1].

During the following year, Dr. Hornykiewicz and his team collected and analyzed more brains from patients without neurological diseases and those who suffered from PD and other neurological disorders. They measured dopamine in those brains and found out that only the PD cases had a severe loss of dopamine in the striatum. This was an important discovery that provided the groundwork for the future research on the mechanisms, causes, and treatment of PD and gave new hope to many PD patients [1].

L-DOPA: AN IMPORTANT NEW DRUG TO TREAT PD SYMPTOMS

The next step for Dr. Hornykiewicz was to find out how to replace dopamine in the brains of PD patients. He knew that dopamine is made from L-dopa (Figure 2), which could be given to humans with no harmful effects. He believed that it should be possible to improve the symptoms of PD by giving L-dopa to patients, but he needed the help of neurologists who were actually treating PD patients. Finally, in July 1961, a neurologist named Dr. Birkmayer injected L-dopa into his PD patients. Dr. Hornykiewicz describes the effects of L-dopa in their first patients as "spectacular." The akinesia in these patients went away!

Figure 4

PD patients often take Levodopa in pill form. The drug is absorbed from the gut into blood and then from the blood to the brain, where it is converted into dopamine.

Figure 4

This research was eventually described in a published report entitled "The L-Dopa Effect on Akinesia in Parkinsonism" [1].

The treatment of PD with L-dopa was a breakthrough in medicine. It was also a triumph for science, because findings of experimental research on animals were successfully used in people. Scientists call this **translation**. L-dopa brought benefits to PD patients because it made their symptoms easier to live with. L-dopa was also used in treatment of some other neurological disorders. It was a great drug behind which there was a great scientist who applied knowledge to connect some unlikely facts and propose a novel solution to the problem of PD.

TRANSLATION

In research, it means an effort to use experimental scientific research to develop new medical therapies or medical procedures.

The drug introduced by Dr. Hornykiewicz is still widely used by PD patients and goes by the name Levodopa (Figure 4). This drug helps millions of PD patients with their symptoms, such as akinesia and tremor but, as we now know, it does not halt the disease. In other words, it is a treatment but not a cure. In some advanced cases of PD, Levodopa is given in high doses and it may cause unpleasant side effects, such as uncontrolled movements. Clearly, even a great drug is not perfect when a disease is as complex as PD.

More research into PD, initiated by the discoveries of Dr. Hornykiewicz, showed that brain cells that produce dopamine and release it into the striatum, die off and disappear in the course of the disease [3]. We call it **neurodegeneration**—Parkinson's disease is a neurodegenerative disorder. PD still needs a cure to protect the dopamine-producing brain cells, so PD research goes on.

NEURODEGENERATION

Progressive death of nerve cells typically starting in one area of the brain and affecting the function of the connected areas. Neurodegenerative diseases include Parkinson's disease.

As we hope you have seen from this article, Dr. Hornykiewicz's work is an impressive example of the successful translation of laboratory-based research into clinical practice in humans. It was a breakthrough in the history of medicine and improved the lives of millions of people with Parkinson's disease, their families and carers. (Reference [4] has been used for the glossary terms).

ACKNOWLEDGMENTS

Research on PD continues with the aim to find a cure. Not only scientists but also patients with PD play an important part in this process as they share their experiences of the disease and its treatment. I dedicate this article to Matt Eagles, who is a lifelong sufferer of PD (in its rare early onset form) and a selfless, tireless patient advocate and public speaker who raises awareness of this disease. I would also like to thank him for his comments on the manuscript, and for his photograph used in Figure 1.

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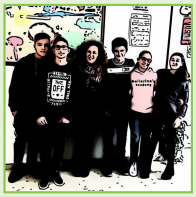

"CORRADINO DI SVEVIA", AGES: 12–13

We are five young science enthusiasts and we are very proud of the work we have done. We are: Salvatore—I like piano, mathematics, science, and history. Gennaro—I like doing nothing but I have a passion for basketball. Tina—I like drawing, art, and English. Carlotta—I really like dance and I also like the Science laboratory. Davide—I

like basketball and playing the guitar. We thank the professors for helping us through this experience. We are confident that this work can be read and understood easily by many students like us.

AUTHOR

JOLANTA OPACKA-JUFFRY

I am a professor of neuroscience in the Department of Life Sciences at the University of Roehampton, in London, U.K. I enjoy doing brain research and am interested in what happens to the brain when it develops a disorder. I did research on Parkinson's disease, for example, how to protect brain cells from dying. I now work on some changes in the brain when it is under too much stress. I like sharing my research findings with students. I also like trees and cats. *j.opacka_juffry@roehampton.ac.uk

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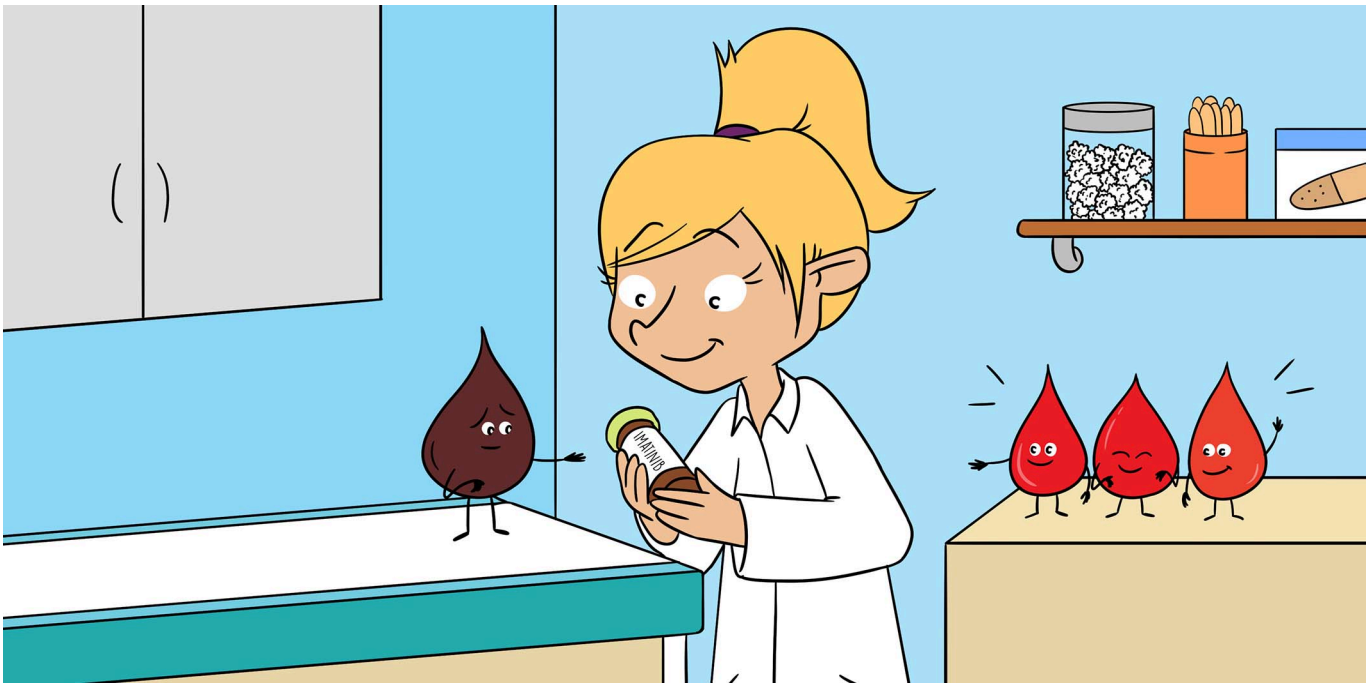

IMATINIB, THE MAGIC BULLET FOR TREATMENT OF BLOOD CANCER

Maria Teresa Esposito *

Health Science Research Centre, University of Roehampton, London, United Kingdom

Some say it is a magic bullet. Others refer to it as a miracle. Imatinib is a drug used to treat a type of blood cancer. Today, patients who take imatinib survive an average of 30 years. This means that most of them can live as long as any other person. This is amazing! In the 1980s, a cancer patient could expect to live only 3–5 years. Imagine how devastating this was for the patient and the patient's family! But how did we develop imatinib? Why is imatinib considered a miracle drug? And why is the story behind this drug so special? To answer these questions, we have to time travel to the past. This article describes the astonishing discovery of imatinib, the magic bullet for treatment of blood cancer, the efforts of the scientists behind this discovery, and what we have learned from the development of this drug.

YOUNG REVIEWER:

VAIGA

AGE: 9

DNA

A very long and tangled material that resembles a ball of wool. It is the material that carries all the information needed for the life and death of a cell.

INTRODUCTION

Since the discovery of **DNA**, the genetic code regulating the life and death of every cell, progress in medicine has flourished. As scientists, we understand diseases better and, therefore, we can develop better

Figure 1

Blood drop in a healthy person and in a leukemic patient. In a blood drop from a healthy person, there are millions of red blood cells, hundreds of thousands of platelets, and thousands of white blood cells. In a leukemic patient's blood, cancer cells, called leukemic cells, emerge and crowd out the other blood cells.

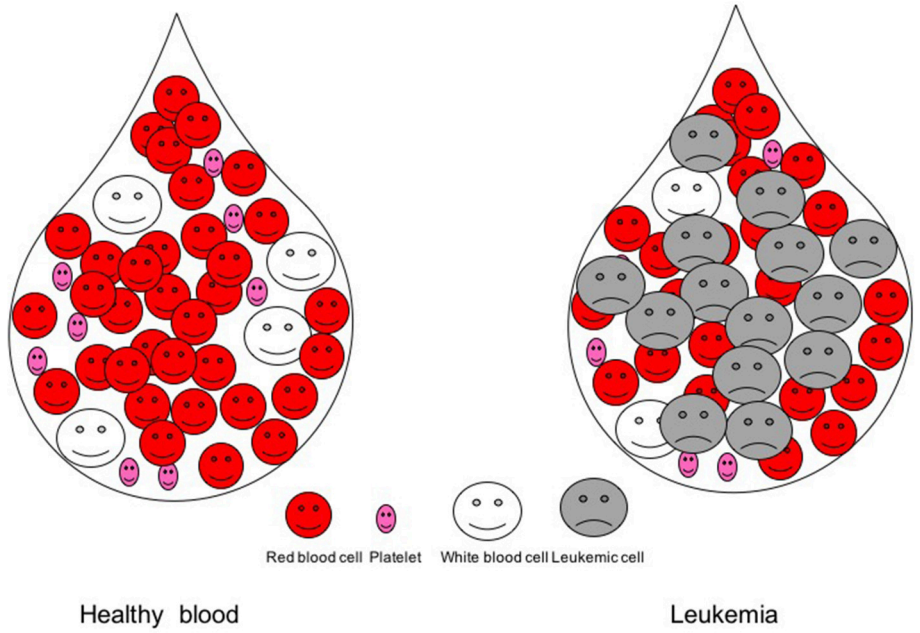

Figure 1

treatments. Cancer is a very serious disease. For decades, doctors have used nasty drugs to treat cancer. Some cancer-treating drugs are nasty because they do not distinguish cancer cells from healthy cells, so they kill both. This means that patients can become sick during the treatment. **Imatinib** is the first drug available to patients that have a rare form of cancer that affects blood cells. In this article, we will tell you about the amazing success of imatinib.

IMATINIB

Is a drug inhibitor of BCR-ABL protein. It binds to BCR-ABL and switches it off.

LET US TALK ABOUT BLOOD CANCER. WHAT IS CHRONIC MYELOID LEUKEMIA?

When you go to the doctor, you tell the doctor your symptoms and expect the doctor to come up with a diagnosis and prescribe you a treatment so that you get better. In 1845, two doctors, Drs. John Bennett in Edinburgh and Drs. Rudolph Virchow in Berlin, had patients whose blood was sick. They did not know what the disease was—it was not in their books. They were the first to describe the symptoms of this new disease. It was a blood cancer that is now known as **chronic myeloid leukemia (CML)** [1, 2].

CHRONIC MYELOID LEUKEMIA (CML)

A blood cancer. In CML patients, the blood is full of cancer cells that occupy all the space normally taken up by functional blood cells.

In the blood, there are three type of cells: red blood cells (erythrocytes) carry oxygen toward the tissues and waste products, such as carbon dioxide, to the lungs; white blood cells (leucocytes) help defend us from infections; platelets (thrombocytes) build a natural plaster to seal up wounds. In CML patients, the blood is full of cancer cells that occupy all the space normally taken up by the useful types of blood cells (Figure 1). This is pretty much all that was known about this disease until 1956.

Figure 2

Chromosomes, genes, and DNA. DNA is a very long, tangled material that resembles a ball of wool. The DNA contains all the information needed for the life and death of a cell. Inside human cells, the DNA is organized into 46 chromosomes. Each piece of information is carried on a different section of the chromosomes. These sections are called genes. Each gene is a unit that encodes for a protein with a specific function.

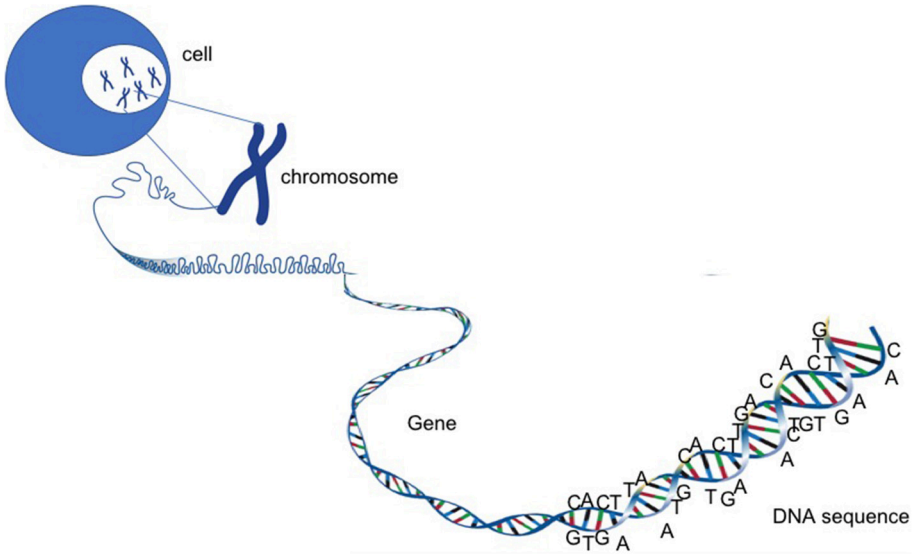

Figure 2

WHAT MAKES BLOOD CELLS GO WRONG? A WEIRD CHROMOSOME

It was only in the late 1950s that scientists started to understand what turned blood cells into CML cancer cells. In 1953, Drs. Rosalind Franklin, James Watson, and Francis Crick discovered the DNA, the genetic code in which all the information about a cell's life resides [3]. The discovery of DNA led to the development of new research areas and methods, which eventually helped scientists understand how DNA is packed into our cells and how it tells cells what to do. After all, if a cell turns into a cancer cell, something must be happening inside the cell that to make it that way!

CHROMOSOMES

Structures made of wound-up DNA. Inside human cells, the DNA is organized into 46 chromosomes. Each chromosome contains hundreds of genes.

In 1956, Drs. Joe Tjo and Albert Levan discovered that human DNA is packed in 46 **chromosomes** (Figure 2). Scientists started to use new methods to view and analyse chromosomes and to compare the chromosomes of cells from healthy people to those from patients affected by various diseases. This way, scientists learned that there are connections between abnormal chromosomes and various human diseases. For example, they discovered that children affected by Down syndrome have an extra copy of chromosome 21. Two scientists, Drs. Peter Nowell and David Hungerford, identified a connection between a chromosomal abnormality and CML. They noticed a strange looking, small chromosome in cancer cells from two patients with this disease. Was this just a coincidence? To answer this question, they analyzed five more patients with the same disease and found the same unusually small chromosome in these patients, too. This small chromosome was soon named the **Philadelphia chromosome**, after the city in which it was discovered (Figure 3).

PHILADELPHIA CHROMOSOME

Is an abnormal small chromosome where a piece of chromosome 22 fuses with a piece of chromosome 9.

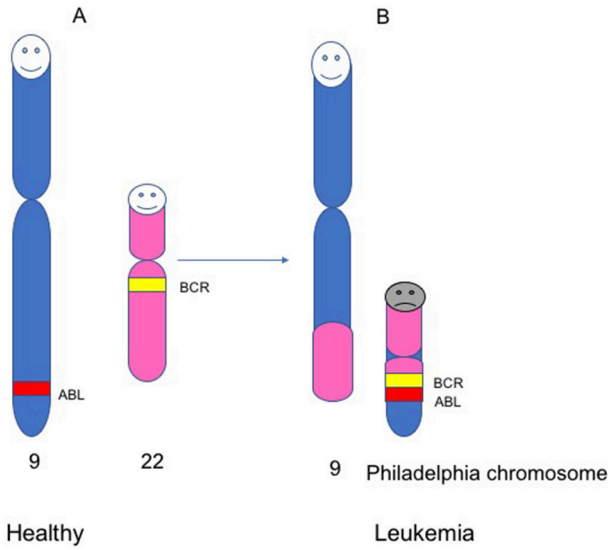

Figure 3

The Philadelphia chromosome. Healthy people carry 23 pairs of chromosomes (46 chromosomes total). **(A)** chromosomes, numbers 9 and 22 in healthy people, and two genes within these chromosomes, ABL and BCR. **(B)** In leukemic patients, there is a change in the structure of chromosomes 9 and 22. During this change, a piece of chromosome 22 fuses with a piece of chromosome 9. This gives rise to a small chromosome called the Philadelphia chromosome, within which the BCR and ABL genes fuse to form a new gene, known as BCR-ABL.

LET US TAKE A CLOSER LOOK INTO THE PHILADELPHIA CHROMOSOME

In the decades following the discovery of the Philadelphia chromosome, scientists became able to study the organization and structure of chromosomes through a microscope. This allowed scientists to understand which pieces of DNA were stuck together in the Philadelphia chromosome. For Dr. Janet Rowley, a biologist at the University of Chicago, it was like doing a jigsaw puzzle. Rowley analyzed cells from nine CML patients and discovered that the Philadelphia chromosome was made from a piece of chromosome 9 glued to chromosome 22 (Figure 3) [4]. As each chromosome is made up of hundreds of **genes**, it was likely that the fusion between chromosomes 9 and 22 fused two genes together. But which genes? It took another 10 years for scientists to answer this question. The conclusion of all these studies was that CML patients had a gene called BCR-ABL, which was created by the fusion of the BCR gene on chromosome 22 and the ABL gene on chromosome 9 (Figure 3).

GENES

The basic unit of DNA. Each gene codes for a protein with a specific function.

BAD GENES MAKE BAD PROTEINS

Why is BCR-ABL bad? In 1990, scientists from the University of California learned the function of the BCR-ABL fusion gene. Genes contain the information needed for a cell to produce **proteins**. In cells, proteins do many things and can take part in cell growth and death. Growth and death are very important, so proteins that play a role in controlling cell growth and death need to be closely regulated. The normal growth of cells is regulated by proteins that work like traffic lights. When the light is green, the cells know that they can grow. When the light is red, the cells understand that they must stop

PROTEINS

The building blocks to make everything in the body.

growing. The BCR-ABL gene produces a protein that keeps the green light on and tells the cells to grow. In CML patients, the blood cells lose control of their growth and grow too fast, which is bad for the patient because the cancer cells crowd out the healthy and functional blood cells (Figure 1).

So, by 1990, scientists knew that the genes BCR and ABL are fused together in the Philadelphia chromosome and make an abnormal protein responsible for the fast growth of blood cells, which causes CML. The fact that CML is due to a single malfunctioning protein meant that drug developers had just one target to look at to cure CML: they had to shut down the BCR-ABL protein and turn the traffic light from green to red.

FROM BASIC SCIENCE TO DRUG DISCOVERY

Unfortunately, in the 1990s, shutting down a protein like BCR-ABL was not easy. There are hundred proteins similar to BCR-ABL in our cells. How could we possibly find a way to shut down BCR-ABL without shutting down all the other proteins, which could kill the patients?

As scientists learned more about the structure of BCR-ABL and similar proteins, they realized that these proteins were slightly different from each other and from BCR-ABL These details were fundamental for designing a drug against BCR-ABL.

An American doctor, Dr. Brian Druker, did some experiments in the laboratory to test possible drugs to treat CML. He found one drug that looked very promising. When he added the drug to the CML cells, they stopped growing. More importantly, when he added the drug to healthy cells, nothing happened. This meant that the drug was safe and did not harm healthy cells. This was exactly what Dr. Druker was looking for! With the help of a British doctor, Dr. John Goldman, Druker encouraged drug companies to produce this drug, which could shut down BCR-ABL.

IMATINIB REACHES CML PATIENTS

Two years later, in 2001, some CML patients took the drug in a clinical trial. Scientists use clinical trials to test new drugs on a small number of patients. The patients are monitored closely, blood tests are done, and if there is any reason to believe that the drug is toxic or is not working, the doctors can quickly stop the treatment. Dr. Druker and colleagues found that the drug killed the cancerous blood cells in nearly all the CML patients [5]. This response was astonishing. It was the first time that doctors observed such a response by administering only *one* anti-cancer drug to their patients, instead of many different,

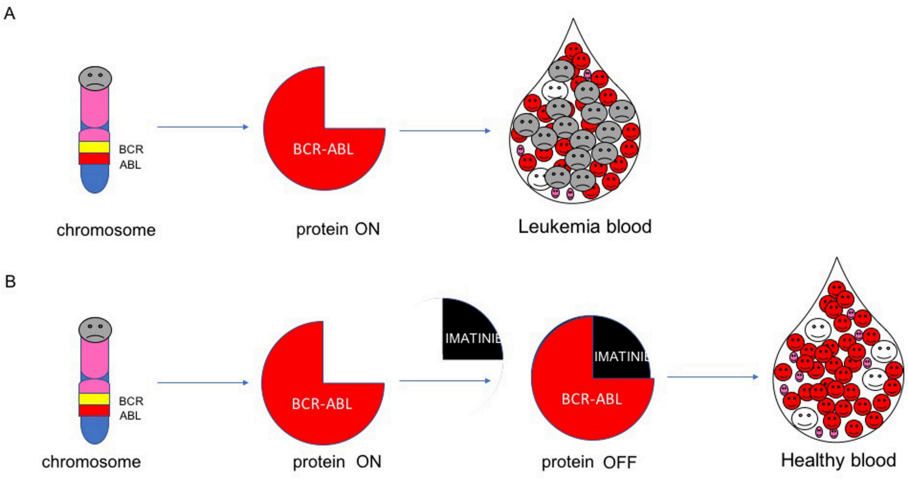

Figure 4

Mechanism of imatinib. **(A)** The BCR-ABL gene encodes for the BCR-ABL protein. When BCR-ABL is switched on, it keeps leukemic cells growing. **(B)** Imatinib switches off BCR-ABL and kills the leukemic cells.

nasty ones! Dr. Druker's team continued to follow the patients for several years. Five years later, the patients still did not have any cancer cells in their blood (Figure 4). These results were impressive!

CONCLUSIONS

Imatinib was a ground-breaking discovery, not only because of the results it achieved and because it saved the lives of thousands of patients, but also because of the way this drug was developed and what scientists have learned from its development. Imatinib taught scientists that, by understanding the biology of a disease—what makes a cell "go wrong" somehow—it is possible to learn how to treat and cure the disease. This approach has since been used to develop drugs for other cancers, such as some forms of ovarian, skin, and lung cancer. It took 41 years from the discovery of BCR-ABL to the development of imatinib. Scientific progress is accelerating the speed of drug development. As scientists, we hope that this progress will more rapidly lead to successful stories, such as that of imatinib. Stay tuned!

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YOUNG REVIEWER

VAIGA, AGE: 9
Fun-loving, sensitive, and inquisitive, always on a quest for something new. Aim to reach the stars.

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Maria Teresa Esposito is a Senior Lecturer in Biomedical Science at the University of Roehampton. She holds a Bachelor degree in Medical Biotechnologies and a Ph.D. in Molecular Medicine. She was trained in hemato-oncology at the Institute of Cancer Research and King's College London. At the University of Roehampton she teaches cellular, molecular biology, and hematology. Her research focuses on mechanisms of chemotherapy resistance of Leukemia and on a particularly aggressive form of leukemia mostly affecting pediatric patients known as Mixed Lineage Leukemia. In 2017 she was awarded the John Goldman Fellowship for translational Hematology.
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HEALTH
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ALEXANDER FLEMING, THE DISCOVERER OF THE ANTIBIOTIC EFFECTS OF PENICILLIN

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YOUNG REVIEWERS:

ANJISHNU
AGE: 12

ENZO
AGE: 15

In 1928, Sir Alexander Fleming observed the bacterial-killing effects of penicillin in his laboratory in London. This was the first step in the discovery of one of the most important pillars of today's medicine: the antibiotics. It took many years to find a way to produce penicillin in large amounts, and large-scale production did not start until 1945. However, to this day, Fleming is considered the father of the antibiotics, and without his discovery we could not treat many infections caused by bacteria. This means that, without antibiotics, even a small infected wound could become fatal. In addition, surgery is much safer with antibiotics, and people with weak immune systems (like children or elderly) can now easily recover from bacterial infections. However, bacteria are becoming resistant to antibiotics, which was also predicted by Fleming in 1945, during his acceptance speech for the Nobel Prize.

TINY FOES AND FRIENDS

Bacteria are very important for us. They live on us and inside us, and we use them to obtain certain nutrients from food, among many other things (Read more in this Young Minds article; We Are Never Alone: Living with the Human Microbiota [1]). But some bacteria, called **pathogens**, can also cause infections and some pathogens can be very dangerous. Pathogenic bacteria are one of the main subjects of microbiology [2], which is the study of microorganisms: tiny forms of life that cannot be seen by the naked eye. Microbiologists have been facing the same questions since bacteria were discovered. How do bacteria infect humans, and most importantly, is there anything that can be done to stop them?

PATHOGEN

A microorganism that invades the body and cause an infection.

An individual bacterium can only be seen with a microscope. However, most bacteria grow well in an environment with lots of nutrients, and broths very rich in nutrients (also known as liquid medium) can be used to grow bacteria [2]. If a test tube with sterile broth and a tiny number of bacteria in it is incubated at a certain temperature, the liquid will become cloudy in a matter of hours and it may even change in color. If a jelly-like substance is added to the broth, and the mixture is heated to melt the jelly, this substance can then be poured on plates (also known as **Petri dishes**) to cool down, you will get a nutrient-rich jelly also known as solid medium. Bacteria can be cultured on the surface of a solid medium. If we add enough bacteria, they will cover the entire surface of the nutrient-rich jelly. If the bacteria are diluted and spread out enough on the plate, an individual bacterium will replicate so much that it will eventually produce a large group of bacteria visible by the naked eye, which we call a **bacterial colony**. If the original source of bacteria contained more than one type, colonies of different kinds of bacteria might be growing on the solid medium. When we touch just one of those colonies with a sterile object and pass the bacteria to a sterile liquid or solid medium, we can produce a pure culture, which should only contain one type of bacteria [2]. Routinely, microbiologists work with pure cultures to be able to reach clear conclusions from their experiments with a single type of bacteria. However, if their work is not done in sterile conditions, the tubes and plates may become contaminated by other bacteria or even some microscopic fungi living in the environment. If that happens, most microbiologists discard that culture and start again. But Fleming was different from most microbiologists.

PETRI DISH

A glass or plastic dish with a lid used to culture living cells.

BACTERIAL COLONY

Group of bacterial cells growing together on the surface of a solid medium that are visible to the naked eye.

AN ACCIDENT WAITING TO HAPPEN...

On the morning of Monday, September 3, 1928, Fleming was coming back from a family holiday [3]. Before he went on holiday, Fleming was working with a very common pathogen: *Staphylococcus aureus*. Fleming left some glass Petri dishes on his lab bench, with these bacteria growing on the surface of solid medium. Usually, these plates

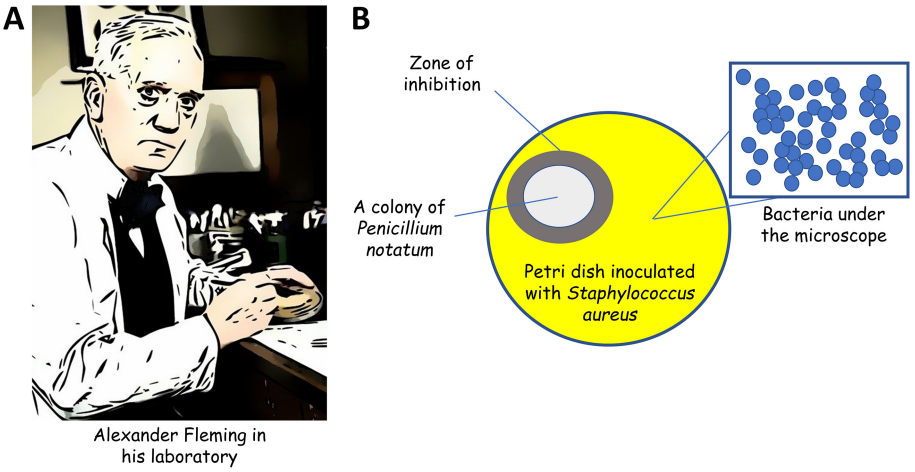

Figure 1

(A) Sir Alexander Fleming at his laboratory bench in London (1943). **(B)** Fleming observed that a colony of a fungus (*Penicillum notatum*) contaminated a Petri dish that was inoculated with *S. aureus*, a dangerous bacterial pathogen. Interestingly, *S. aureus* was unable to grow in the area surrounding the colony of *P. notatum*. Fleming deduced that the fungus was producing something that killed *S. aureus* in the zone of inhibition.

would be sterilized by a laboratory technician to reuse them in other experiments. However, Fleming always had a final look at all his experiments before discarding them, even if they were kept for weeks on the bench (Figure 1A). He would randomly pull samples from the stack of plates to see if anything interesting happened during the last few weeks. Because his laboratory was quite primitive, Fleming would commonly have contaminations on his plates, which were often caused by yeasts and molds from the environment. But one plate looked very different, and when he noticed that plate, he famously said "That is funny...." The plate had been inoculated with a dense culture of bacteria, but it was also contaminated with a microscopic fungus that created a big colony on the side of the plate. What was unusual was that the bacteria were not able to grow in the area close to the fungus colony. There was a perfectly visible area surrounding the fungus that was completely free of bacteria; today, we call this a **zone of inhibition** (Figure 1B). Therefore, Fleming discovered that a fungus (*Penicillium notatum*) was producing something that killed *Staphylococcus aureus*, a dangerous pathogen. Fleming had just discovered an antibiotic, and at first, he called this "mold juice" [3].

ZONE OF INHIBITION

Area surrounding the source of an antibiotic in which bacterial colonies do not grow.

At that time, neither Fleming nor his colleagues thought that this discovery could have any real importance, and the actual importance was only demonstrated more than a decade later. However, Fleming had just discovered the biological warfare that exists between different microorganisms fighting for space in an environment rich in nutrients [2]. Fleming did not create penicillin, he observed that a colony of a microscopic fungus produced penicillin as a way to compete with bacteria for the nutrients on an almost-discarded plate. Since then, microbiologists have searched in nature for new antibiotics, to test whether any other microorganisms can produce antibiotics, and this approach has been very successful. Once a new antimicrobial substance is identified, that substance is purified and may be chemically modified to make it easier to produce the new antibiotic

in large quantities, or to create new versions of the original substance. We are still looking for new antibiotics, and anyone can be part of this through initiatives like "Swab and Send" [4].

HOW DOES PENICILLIN WORK?

The way that penicillin works to inhibit bacterial growth was not understood until 1980. Now we know that penicillin inhibits the activity of certain enzymes in bacteria called penicillin-binding proteins (PBPs), which are essential for most bacteria to create a wall that covers their cells. Without that wall, bacterial cells are much more exposed the environment, and they may die very easily when the environment changes. In the presence of penicillin, bacteria cannot produce this cell wall to protect themselves, and they die. Penicillin is part of a family of similar antibiotics called the β-lactams, and many bacteria become resistant to β-lactams either by producing enzymes that degrade these antibiotics or by acquiring modified versions of the PBPs that do not bind to penicillin any more [2].

THE RESISTANCE IS RISING...

What Fleming also predicted during his speech accepting the Nobel Prize in 1945 was that bacteria may become resistant to antibiotics. This is just happening due to evolution, because bacteria can adapt very quickly to overcome any hurdle limiting their growth. The changes that help bacteria to adapt may be driven by random mutations in their DNA, and the process is really fast—you can almost see this happening in real time! [5]. In addition, many of the microorganisms producing antibiotics also have genes that make them resistant to those antibiotics. Bacteria are very good at acquiring DNA from other organisms, to get new abilities. This is called horizontal gene transfer [2]. If pathogenic bacteria acquire the genes to make them resistant to a specific antibiotic, that antibiotic becomes useless in the clinic. To prevent antibiotic resistance, antibiotics should only be used when needed (for instance, viruses cannot be killed by antibiotics, so they should not be taken for viral infections), the correct dose should be used (because too low of a dose may help create resistant strains), and we should take antibiotics for the entire time they are prescribed, to make sure to kill all the bacteria causing the infection. If we do not take these steps, we might be helping the spread of antibiotic resistance, and this is a huge problem. In fact, the most dangerous bacterial pathogens are becoming resistant to many antibiotics [2]. Drug manufacturing companies are losing interest in developing new antibiotics, because these drugs may not be profitable as antibiotic resistance grows. Consequently, the rate at which new antibiotics are discovered is not fast enough to cope with the emergence of new, antibiotic-resistant pathogens. We may soon

go back to a pre-antibiotic era, in which people infected with bacteria could not be treated effectively.

CONCLUSION

The discovery of penicillin was only possible in a laboratory where contaminations were common. Chance certainly played a role in the discovery of the first antibiotic, but the training and laboratory practice of Fleming were essential for him to identify one of the most important drugs in human history. Unfortunately, due to antibiotic resistance, microbiologists are in a race with bacterial pathogens to find new ways to treat infections. Today, we have a better understanding of how pathogens interact with their hosts, how antimicrobials work, and what the mechanisms of antibiotic resistance are. But, even 90 years after the discovery of penicillin, there is still much more work needed to combat the current antibiotic crisis. You can be part of this by participating in the Swab and Send initiative!

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YOUNG REVIEWERS

ANJISHNU, AGE: 12

Hello, my name is Anjishnu and I am in sixth grade. I live in San Diego and I have a passion in writing, reading, math, and science. I also like reading about cars and other vehicles. I enjoy playing tennis and guitar. I want to be an aeronautical engineer when I grow up and would like to design planes that will make flying safer.

ENZO, AGE: 15

Enzo is currently coursing the first year of High School. He is planning to study Computational Engineering at college. He is fascinating by the English culture and has visited many places in the United Kingdom. He was aware of Fleming's discovery, and visited the Fleming museum in London.

AUTHOR

MICHAL LETEK

My research work has always been focused on identifying new ways to control bacterial pathogens. Over the last few years, I have studied how bacteria grow and divide, how they interact with their host during infection, and the host response to bacterial infection. My aim is to find novel therapies to control bacterial pathogens and to understand what makes us susceptible to infections caused by microorganisms, such as *Staphylococcus aureus* or *Mycobacterium tuberculosis*. *michal.letek@unileon.es

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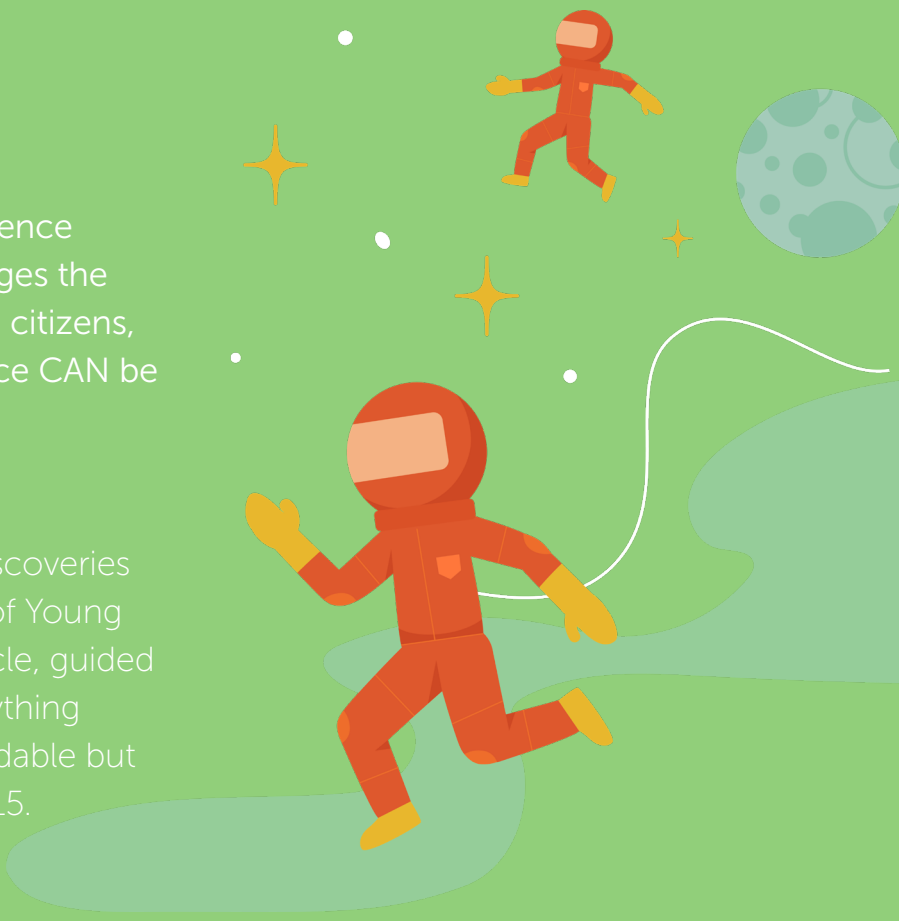

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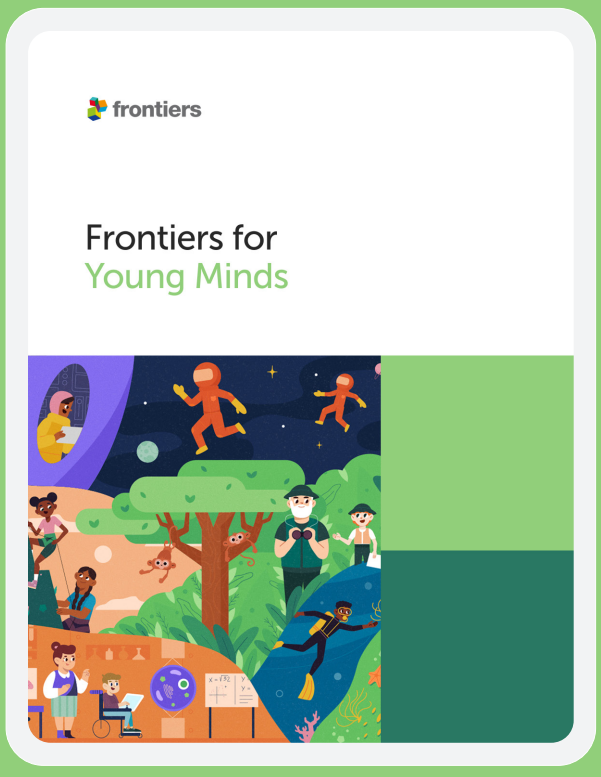

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