ARTÍCULO DE REVISIÓN

ALEXANDER FLEMING AND THE ANTIBIOTIC REVOLUTION

ALEXANDER FLEMING Y LA ERA DE LOS ANTIBIÓTICOS

Alejandro Pérez Capote[1*], Ana Laura Taillacq Suárez[1], Marcos Manuel Marin Gutiérrez[2], Bruna Rosario Quevedo Almarales[3]

[1]Estudiante de tercer año de la carrera de Medicina. Alumno ayudante de la especialidad de Cirugía General. Universidad de Ciencias Médicas de Cienfuegos.
[2]Estudiante de tercer año de la carrera de Medicina. Alumno ayudante de la especialidad de Cirugía Pediátrica. Universidad de Ciencias Médicas de Cienfuegos.
[3]Licenciada en Lenguas Extranjeras Inglés. Máster en Ciencias de la Educación. Profesor instructor. Universidad de Ciencias Médicas de Cienfuegos.

Correspondencia*: medapc980614@ucm.cfg.sld.cu

RESUMEN

La introducción y aplicación de antibióticos ha sido uno de los grandes avances en de la medicina hoy día; el primero que se utilizó fue la penicilina por Alexander Fleming en el siglo XX. El presente trabajo tuvo como objetivo describir la enorme contribución realizada por Alexander Fleming a la medicina, resaltando sus extraordinarios descubrimientos. Para ello se consultó un total de 20 fuentes bibliográficas, que incluyen 16 artículos de revistas científicas de impacto internacional, 4 libros y otras accedidas a través de los principales gestores de la red informática. Se concluyó que Alexander Fleming revolucionó el mundo de la medicina, su descubrimiento de las lisozimas y la penicilina trajo una nueva esperanza a la humanidad en su lucha contra ciertas enfermedades, y en el tratamiento de infecciones bacterianas.

Palabras clave: Alexander Fleming, antibióticos, lisozimas, penicilina.

ABSTRACT

The introduction and application of antibiotics has been one of the greatest breakthroughs in medicine to date; the first one used was penicillin by Alexander Fleming in the 20th century. The main aim of this investigation was to describe the enormous contribution made by Alexander Fleming to medicine, highlighting his outstanding discoveries. A total of 20 bibliographical sources were consulted for the investigation, including 16 scientific journals with a high international impact, 4 books and other sources that were accessed through the main managers of the information network. It was concluded that Alexander Fleming revolutionized the world of medicine, his discoveries of lysozymes and penicillin brought new hope to mankind in fighting certain diseases and treating bacterial infections.

Key words: Alexander Fleming, antibiotics, lysozymes, penicillin

INTRODUCTION

Medicine touches us all at some stage in our lives. Whether we live in a crowded high-tech westernized society that uses the diagnostic and therapeutic tools of modern bioscience or in an isolated rural community where health care is perhaps less formal, less intrusive and less commercial, it is arguably medicine, rather than religion or law, that dictates the manner in which we are born, the quality of our lives, and the ease and speed of our deaths. Indeed, although modern populations are increasingly struggling to handle with chronic conditions such as cancer, heart disease, arthritis, obesity and depression, we have come to rely heavily on the ability of medicine to help us live relatively happily, healthily and productively well into our eighties. [1,2]

Developments in the fields of surgery, medical technology and pharmacology have facilitated treatment of a wide range of malignant and non-malignant diseases that were previously untreatable. These advances have led to an increased life expectancy and quality of life. Nevertheless, there is a downside, consisting of a surge in the number of patients who are particularly vulnerable to infection because of surgical and other invasive procedures, treatment with immunosuppressive drugs or simply aging of the immune system. These patients may become infected with a wide range of microorganisms, including those that are not normally pathogenic. [2,3]

Microbiology is the science that studies these microorganisms and it has had a long, rich history, initially centred in the causes of infectious diseases but now including practical applications of the science. There is an endless list of microbiologists that have made immeasurable contributions to this discipline; most of them revolutionized medicine in the 20th century. One of its greatest breakthroughs are antibiotics and the first one used was penicillin, in 1928 by Alexander Fleming. [3,4] The impact of penicillin has allowed doctors to save millions of lives and it has prevented hundreds of diseases. Fleming's work renewed interest in the search for antibiotic compounds with similar efficacy and safety. Due to the importance of this work, we aim to describe the enormous contribution made by Alexander Fleming to medicine, highlighting his outstanding discoveries.

DEVELOPMENT

Alexander Fleming was born on August 6th, 1881 at Lochfield farm near Darvel, in Ayrshire, Scotland. He was the third of the four children of farmer Hugh Fleming from his second marriage to Grace Stirling Morton, the daughter of a neighboring farmer. Hugh Fleming had four surviving children from his first marriage. He was 59 years old at the time of his second marriage, and died when Alexander was 7 years old, leaving his wife to manage the farm with her eldest stepson. [5]

Alexander began his elementary schooling when he was 5 years old at the tiny Loudoun Moor School where 12 pupils of all ages were taught in a single classroom. Darvel School was his next step, which involved an eight-mile round trip on foot every school-day. At the age of 11 his academic potential was recognized and he was awarded with a two-year scholarship to Kilmarnock Academy. [5,6]

In 1895 he moved to London at the age of thirteen, to live with his elder stepbrother Thomas who was already a physician. There he attended the Royal Polytechnic Institution, where he studied business and commerce. He started in a class appropriate to his age, but his teachers soon realized he needed more challenging work. He was moved into a class with boys two years older than him and finished school at the age of 16. Alexander's business training helped him to get a job in a shipping office as a clerk; he worked there for four years, but he did not enjoy it at all. [5,6]

In 1900 he enlisted in the London Scottish Regiment and he served briefly in the army during the Boer War, it ended before he got overseas. He enjoyed life in the ranks and stayed attached to this regiment until 1914. Fleming was short but sturdy; he had a fair complexion, with blue eyes, good at rifle shooting and water polo. [7]

When he was 20 years old, Fleming inherited some money from an uncle, John Fleming, and he decided to study medicine. First, he needed

suitable qualifications to enable him to enroll at medical school, but it was not a problem; he passed his exams with the highest marks of any student in the United Kingdom. In 1903, Alexander enrolled at London's St Mary's Hospital Medical School, graduating with distinction three years later as Bachelor of Medicine, Bachelor of Surgery. [5]

Fleming had been a private since he was 19 years old and he became a member of the rifle club at the medical school. The captain of the club, wishing to retain Fleming in the team, suggested him to join the research department at St Mary's, where he became assistant bacteriologist to Sir Almroth Wright, a pioneer in vaccine therapy and immunology. While carrying out this research Fleming graduated, in 1908, with a degree in Bacteriology and the Gold Medal for top student. St Mary's Hospital Medical School then promoted him to the role of bacteriology lecturer until 1914. [7,8]

Almroth Wright turned over to Fleming samples of a new drug, Salvarsan, synthesized by Paul Ehrlich and colleagues for treating syphilis. Fleming's experience administering the drug to patients was positive, and thereafter he maintained a small but lucrative practice administering Salvarsan to wealthy patients suffering from syphilis. [8]

In 1914 World War I broke out and Fleming joined the army, becoming a captain in the Royal Army Medical Corps working with many of his colleagues in battlefield hospitals at the Western Front in France. [9,10]

There, in a series of brilliant experiments, he established that antiseptic agents used to treat wounds and prevent infection were actually killing more soldiers than the infections were. The antiseptics, such as carbolic acid, boric acid and hydrogen peroxide, worked well on the surface, but were failing to kill bacteria deep in wounds; worse, they were in fact lowering the soldier's natural resistance to infection because they were killing white blood cells. [10,11]

Fleming demonstrated that antiseptic agents were only useful in treating superficial wounds, but were harmful when applied to deep wounds. Almroth Wright believed that a saline solution should be used to clean deep wounds, because this did not interfere with the body's own defences and in fact attracted white cells. Fleming proved this result in the field and together they published their results in an article he submitted for the medical journal The Lancet, but most army doctors refused to change their ways, resulting in many preventable deaths. [11]

In 1918 he returned to St Mary's Hospital, where he was promoted to Assistant Director of the Inoculation Department. In November of 1921, Fleming had taken secretions from inside the nose of a patient suffering from a head cold. He cultured the secretions to grow any bacteria. In the secretions, he discovered a new bacterium he called Micrococcus lysodeikticus, now called M. luteus. A few days later, Fleming was examining these bacteria, but he was suffering from a head cold, and a drop of mucus fell from his nose on to the bacteria. The bacteria in the area where the drop fell were almost instantly destroyed. Always on the lookout for natural bacteria killers, this observation excited Fleming enormously. [10,12]

He tested the effect of other fluids from the body, such as blood serum, saliva, and tears, on these bacteria and found that bacteria would not grow where a drop of one of these fluids was placed. Fleming discovered the common factor in the fluids was an enzyme. He named his newly discovered enzyme lysozyme. [3]

The effect of lysozyme was to destroy certain types of microbe, rendering them harmless to people. The presence of lysozyme in our bodies prevents some potentially pathogenic microbes from causing us harm. It gives us natural immunity to a number of diseases. However, lysozyme's usefulness as a medicine is rather limited, because it has little or no effect on many other microbes that infect humans. Fleming had discovered a natural antibiotic that did not kill white blood cells. [9,13]

By 1927, Fleming had been investigating the properties of Staphylococcus. He was already well-known from his earlier work, and had developed a reputation as a brilliant researcher, but his laboratory was often untidy. On Monday, September 3th, 1928, Fleming returned to his

laboratory having spent August on holiday with his family. Before leaving, he had stacked all his cultures of Staphylococcus on a bench in a corner of his laboratory. On returning, Fleming noticed that one culture was contaminated with a fungus, and that the colonies of Staphylococcus, immediately surrounding the fungus, had been destroyed, whereas other Staphylococcus colonies farther away were normal. [14]

Somehow, in preparing the culture, a mould spore had been accidentally introduced into the medium—perhaps coming in through a window, or more likely floating up a stairwell from the lab below where various moulds were being cultured. The temperature conditions that prevailed during Fleming's absence permitted both the bacteria and the mould spores to grow. [14,15]

Excited by his observation, Fleming showed the Petri dish with the contaminated culture to his former assistant Merlin Price, who reminded him, "That's how you discovered lysozyme." [15]

Hoping he had discovered a better natural antibiotic than lysozyme, Fleming grew the mould in a pure culture and found that it produced a substance that killed a number of disease-causing bacteria. He identified that the antibacterial substance was not produced by all moulds, only by certain strains of Penicillium, and after some months of calling it "mould juice", he formally named the antibiotic penicillin on March 7th, 1929. He studied methods of producing the impure product and determined its stability at different temperatures and over various lengths of time. He investigated its effect on many microbes; he tested its toxicity on a laboratory mouse and a rabbit. [8,15,16]

Fleming published his discovery in 1929, in the British Journal of Experimental Pathology, showing that penicillin killed many different species of bacteria and it was non-toxic and it did not attack white blood cells, but little attention was paid to his article. [16]

Fleming continued his investigations, but found that cultivating Penicillium was quite difficult, and that after having grown the mould, it was even more difficult to isolate the antibiotic agent. Fleming's impression was that because of the problem of producing it in quantity, and because its action appeared to be rather slow, penicillin would not be important in treating infection. [12,14]

By 1932, he had effectively abandoned his research on penicillin. However, in 1939, a team of scientists at Oxford University began to work on trying to make a large quantity of antibacterial agents. The team under Howard Florey and Ernst Chain started to work using Fleming's penicillin culture. After the team had developed a method of purifying penicillin to an effective first stable form in 1940, several clinical trials ensued, and their amazing success inspired the team to start producing the world's first antibiotics by developing methods for mass production and mass distribution in 1945. The antibiotic eventually came into use during World War II, revolutionizing battlefield medicine, it also helped to eradicate many bacterial infections such as pneumonia, syphilis, gonorrhoea, diphtheria, scarlet fever and many childbirth infections. [7,14,15]

Alexander Fleming, Florey and Chain collectively received the Nobel Prize in Medicine in 1945. The award was made "for the discovery of penicillin and its curative effect in various infectious diseases." This year he visited America, where chemical companies offered him a personal gift of a hundred thousand dollars, as a mark of respect and gratitude for his work. Typically of Fleming, he did not accept the gift for himself: he donated it to the research laboratories at St Mary's Hospital Medical School. He said: *"When I woke up just after dawn on September 28th, 1928, I certainly didn't plan to revolutionise all medicine by discovering the world's first antibiotic, or bacteria killer. But I suppose that was exactly what I did"* [17,18]

Fleming's discovery of penicillin changed the world of modern medicine by introducing the age of useful antibiotics; it was enormously recognized all over the world. He was a member of the Pontifical Academy of Sciences; he was elected a Fellow of the Royal Society in 1943. Fleming was awarded the Hunterian Professorship by the Royal College of Surgeons of England and he was knighted, as a Knight Bachelor, by King George VI in 1944. Besides, he was awarded with numerous foreign decorations and medals, honorary

memberships in medical and scientific societies, and doctorates from famous universities. He was elected president of the newly founded Society for General Microbiology in 1945 and rector of Edinburg University in 1951. He was also awarded doctorate, *honoris causa,* degrees of almost thirty European and American Universities. [10,18,19]

Even though Fleming spent most of his life studying, investigating and working to improve people's health, he never neglected his family and his personal life. On December 24th, 1915 Fleming married Sarah Marion McElroy, an Irish farmer's daughter, who had operated a private nursing home. Despite their dissimilar characters, the marriage was happy. They enjoyed gardening at their Suffolk country house, were very hospitable, and collected antiques. Their only child, Robert, born in 1924, became a physician. Fleming's wife died in 1949, and then he married Amalia Coutsouris-Voureka, a Greek bacteriologist working in his research group at St Mary's Hospital Medical School, on April 9th, 1953. [18,19]

On March 11th, 1955 at the age of 73, Alexander Fleming died from a heart attack in London. His ashes were placed in St Paul's Cathedral. [19]

The world has continued honouring Fleming, even after his death. The laboratory at St Mary's Hospital where Fleming discovered penicillin is home to the Fleming Museum, a popular London attraction. In 1999, Time magazine named Fleming one of the 100 Most Important People of the 20th century and at least three large Swedish magazines ranked penicillin as the most important discovery of the millennium. Many statues of Alexander Fleming have been erected, as well as many squares and schools have been named after him; stamps have been cancelled commemorating Fleming and 91006 Fleming, an asteroid in the Asteroid Belt, and a lunar crater were also named after him. [10,16,20]

CONCLUSIONS

Sir Alexander Fleming changed the world of medicine not only in his days but also in the world today. For the last decade of his life, Fleming was famous all around the world for his discovery of penicillin and acted as a world ambassador for medicine and science. Initially a shy uncommunicative man and a poor lecturer, he blossomed under the attention he received, becoming one of the world's best-known scientists. His discoveries brought new hope to mankind in fighting certain diseases and treating bacterial infections. We have the medicines and antibiotics that we have today because of Alexander Fleming, and we hate to think where we would be in the medicine world if he hadn't discovered penicillin.

BIBLIOGRAPHICAL REFERENCES

1. Bârsu C. History of Medicine between tradition and modernity. Clujul Med [Internet]. 2017 (cited 2018 Apr 4) ;90(2):243-245. Available from: DOI: 10.15386/cjmed-794; PubMed PMID: 28559713; PubMed Central PMCID: PMC5433581.
2. Rosen GA History of Public Health. Baltimore: Johns Hopkins University Press Books; 2014.
3. Cameron DE, Bashor CJ, Collins JJ. A brief history of synthetic biology. NatRev Microbiol [Internet]. 2014 May (cited 2018 Apr 4);12(5):381-90. Available from: DOI: 10.1038/nrmicro3239; PubMed PMID: 24686414.
4. Adedeji WA. The treasure called antibiotics. Ann Ib Postgrad Med [Internet]. 2016 Dec (cited 2018 Apr 6);14(2):56-57. Available from: PubMed PMID: 28337088; PubMed Central PMCID: PMC5354621.
5. Macfarlane G. Alexander Fleming: The Man and the Myth. Oxford: Oxford University Press Books; 2010.
6. Goldsworthy PD, McFarlane AC. Howard Florey, Alexander Fleming and the fairy tale of penicillin. Med J Aust [Internet]. 2002 (cited 2018 Apr 8);176(4):176-8. Available from: PubMed PMID: 11913920.
7. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T [Internet]. 2015 (cited 2018 Apr 8);40(4):277-83. Available from: PubMed PMID: 25859123; PubMed Central PMCID: PMC4378521.
8. Alharbi SA, Wainwright M, Alahmadi TA, Salleeh HB, Faden AA, Chinnathambi A.What if Fleming had not discovered penicillin? Saudi J Biol Sci [Internet]. 2014 (cited 2018 Apr 9);21(4):289-93. Available from: DOI:

10.1016/j.sjbs.2013.12.007; PubMed PMID: 25183937; PubMed Central PMCID: PMC4150221.
9. Dosan S. Penicillin Man: Alexander Fleming and the Antibiotic Revolution. BMJ [Internet]. 2005 (cited 2018 Apr 9); 330(7481): [aprox. 19 p.]. Availalable from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC539899/
10. Bârsu C. History of Medicine between tradition and modernity. Clujul Med [Internet]. 2017 (cited 2018 Apr 12);90(2):243-245. Available from: DOI: 10.15386/cjmed-794.; PubMed PMID: 28559713; PubMed Central PMCID: PMC5433581.
11. Tan SY, Tatsumura Y. Alexander Fleming (1881-1955): Discoverer of penicillin. Singapore Med J [Internet]. 2015 (cited 2018 Apr 12);56(7):366-7. Available from: DOI: 10.11622/smedj.2015105. PubMed PMID: 26243971; PubMed Central PMCID: PMC4520913.
12. Alberts B. A grand challenge in biology. Science [Internet]. 2011 (cited 2018 Apr 12);333(6047):1200. Available from: DOI: 10.1126/science.1213238. PubMed PMID: 21885740.
13. Ma'ayan A. Complex systems biology. J R Soc Interface [Internet]. 2017 (cited 2018 Apr 12);14(134). Available from: DOI: 10.1098/rsif.2017.0391; PubMed PMID: 28931638; PubMed Central PMCID: PMC5636275.
14. Lou C, Stanton B, Munsky B. The greatest antibiotic contribution: Alexander Fleming. Nature Biotech [Internet]. 2014 (cited 2018 Apr 13); 30(2): 55-63. Available from: https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html
15. Kissick WL. The Life of Sir Alexander Fleming, Discoverer of Penicillin. Yale J Biol Med [Internet].1959 (cited 2018 Apr 13); 32(2): [aprox. 23 p.]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2604061/
16. Bengtsson B. Alexander Fleming: Pioneer with Antibiotics. Washington: McJohn's; 2009
17. Cruickshank R. A Brief Biography of Alexander Fleming. American Journal of Medicine [Internet]. 2016 (cited 2018 Apr 15); 31(3): 12-16. Available from: http://journals.sagepub.com/doi/abs/10.1177/096777200401200105
18. Brown K. Penicillin Man. The New England Journal of Medicine [Internet]. 2015 (cited 2018 Apr 15); 24(1): 12-14. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5433581/
19. Hare R. The Cambridge Illustrated History of Medicine. Cambridge: Cambridge University Press Books; 2014
20. Lewine E. Florey and the development of penicillin. Journal of Clinical Investigation [Internet]. 2015 (cited 2018 Apr 16); 14 (2): 4-7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC539899/

Cita del artículo:
Pérez Capote A, Taillacq Suárez AL, Marin Gutiérrez MM. Alexander Fleming and the antibiotic revolution. INMEDSUR [Internet]. Nov 2018-Feb 2019; 1 (1): 72-77.