Vincenzo Tiberio, interspecies competition and infection control strategies

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Abstract

The following paper sums up the history of Dr. Vincenzo Tiberio, a military physician from Italy, who lived around the second half of the past century. His life was dedicated to clinical research, particularly in the context of microorganism competition and mechanisms of transmission of infections. His scientific work, though significant and innovative, was adequately appreciated just many years after his death; a great loss for the scientific world since his discovery could have laid the groundwork for the development of antimicrobial drugs that can be used nowadays in the infection control strategies.

Introduction

For thousands of years, mankind has been exposed helplessly to a broad range of infectious diseases, which often reach outbreak and pandemic scale and result in the death of a billion humans.[1] People from all over the world have tried to define mechanisms behind their onset and to find remedies and strategies to prevent and cure them. Over the centuries, all these efforts have led to the discovery of pathogens as responsible for most of the infections, and to the development of antimicrobial therapies, which nowadays are set up as the main weapon in our clinical practice against infectious diseases. Currently, we can find many different pharmacological classes, capable of countering a broad spectrum of pathogens on different tissue targets; they are the result of a process whose steps are plotted in the following chapter.[2]

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Steps of antibiotics history

Since the Egyptian age, and through the ancient Greece and Roman Empire, it was commonly known that mold could be used as a remedy for different medical conditions: Arabian and European medieval doctors used to prepare healing compounds with mold and musk, which they put on wounds to make them close and not infect, as the English royal apothecary John Parkingson later confirmed in 1640.[1] We have to move forward two centuries, before another illustrious scientist, Louis Pasteur, put another piece on this puzzle with his idea of "microorganisms antagonism", according to which the competition between living beings can be so strong that there is often one who overrides the others.[4] This a concept that Professor Arnaldo Cantani from Naples applied to his tuberculosis patients, making them inhale a bacterial culture watching some of them heal, and fighting for the first time a bacterial infection with bacteria.[3] A concept, furthermore, that Paul Vuillemin took up in his scientific report "Antibiose and Symbiose" for the 'French Society for Scientific Progress', in 1889.[4]

The most popular step on this route is the discovery of Penicillin in 1929 by Sir Alexander Fleming, and subsequent large-scale production since the 40s.

What is still not certainly known, is whether Fleming knew that thirty years before another scientist was on the trail of the same discovery.[5]

Dr Vincenzo Tiberio: the story of his experiments

Vincenzo Tiberio was a physician of the Italian army, who lived between 1869 and 1915. He came from Sepino, near Campobasso (Italy), and went to Naples to study medicine when he was 19. After he finished university, he became assistant to Vincenzo de Giaxa, Director of the Hygiene Institute at Naples University, and started to work in the laboratory of the Institute, under the direct supervision of Professor Arnaldo Cantani.[3] During these years, he stayed with his relatives in Arzano and had

the habit of picking water up from a hole near the house for the whole family. It was this habit, blended with the scientific environment where he was working, that led to a first observation: he noticed that the family developed dysentery when the hole he picked water from was clean. To assess if the water was potable or not, he took a sample and tried to analyze it, and to his great surprise, he discovered that it was completely sterile. Unsure about his findings, he went back to the hole, and he noticed that its walls were completely covered by a thick layer of mold.[6]

And that was the revolutionary question he asked himself: would it be possible for the mold to protect from gastrointestinal infections caused by the water, and cleaning the hole would reverse this effect?

The cornerstones of his discovery – a draft of the scientific method

Doctor Tiberio, starting from this theory, brought his study forward with a rational and scientific approach: after observing the phenomenon, first of all, he took a sample of the mold and analyzed it through the microscope and on a breeding ground. What he found out was that the mold was made of three types of fungi: *Aspergillus flavescent*, *Penicillium glaucum*, and *Mucor mucedo*.[6] From this evidence, he determined his main questions: i) how could it be demonstrated that these fungi make the water safe? ii) is this antibacterial activity repeatable and suitable for fighting infections?

What he did was take a sample of a watery product of the culture and test out its antimicrobial power in vitro and in vivo.

In vitro study

He put the watery product of the mold and a bacterial extract of *Vibrio cholerae* (as above) and *Salmonella typhi* in the same culture ground and assessed that the bacteria did not grow up.[6]

In vivo study

HE took some test subjects and split them into groups: i) in some groups, he injected subcutaneously the bacteria and the mould extract in two different concentrations at the same time; ii) in some others, he injected the mold extract hours or days before the injection of the bacteria; iii) alongside, he studied the chemotactic activity of the product of the different fungi after subcutaneous or intraperitoneal injection.[3]

As he later wrote in his paper, the starting point of his research was that "in the process of evolution of organic matter, much is represented by a widespread and interesting group of Schizomycetes, no less important are fungi of a higher order, that at times seem to hinder, in competition for life, the development of Schizomycetes".[3,6]

His work brought him to the discovery that the watery product of the mold was effective in countering bacterial growth when injected at the same time or at most eight days before; that it was able to fight bacteria through both direct antibacterial and chemotactic activity, and that *Aspergillus flavescens* was able to induce the most powerful chemotaxis, stressing out the importance of white cells in fighting infections.[6]

At the end of his work, which was finely and precisely documented with tables of the dates and an accurate description of the method, he reproduced the experiments with other pathogenic organisms, and once he found the same results, he published them in *the Annals of experimental hygiene* in 1895.[6]

Despite the quality of his work, which represented a fine assumption for new relevant scientific discoveries, the academic world did not take it into account and unfortunately, shortly thereafter, Dr. Tiberio had to join the army. Consequently, he could not move after his discovery, which he managed to take up again only a few years later, just before his death.

His study was resumed by Dr. Giuseppe Pezzi only in 1947, two years after the award of the Nobel Prize, in 1945, to Alexander Fleming; whether or not the latter was informed of Tiberius' studies is still a debated point.[5,7,8]

Discussion and Conclusions

The authors consider Tiberius' experience to offer extremely topical insights.

Firstly, an emergency physician, even in the third millennium, needs to understand the fundamentals of the basic sciences. Tiberius' methodology also offers a useful reminder of the path of medical knowledge.

Moreover, Tiberius' experience serves as a paradigm of the equilibrium between different microorganism species.

Intensive and sub-intensive care units face the challenges of MDR microorganisms daily.[9]

Microbial competition processes are among the key factors behind the selection and spread of MDR microorganisms.[10,11]

Previous therapy with broad-spectrum antibacterial drugs is a risk factor for MDR germ infections, most likely due to the impact on microbial competition mechanisms.[12-14]

The authors deem these topics to be of paramount relevance. Clinicians should be aware of these principles and translate them into clinical practice.

Modern antimicrobial treatment approaches take these insights into account.[9,15,16] Bacterial competition should be a topic of antimicrobial stewardship programs and should be taken into account in infection control strategies.[21]

Secondly, regardless of the specific case, the affair should lead us to some considerations: should we take more into count the work and ideas of every colleague? Sometimes the greatest wisdom lies in unexpected places and if we were positively disposed toward their opinions, we would notice that good ideas can be found anywhere. Furthermore, should we rewrite history? Despite the many possible opinions about it, Dr. Vincenzo Tiberio set the groundwork for the principles of antibiotic therapy thirty-four years before Dr. Fleming discovered penicillin, and he consequently qualifies as a pioneer of our never-ending fight against infectious diseases.

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