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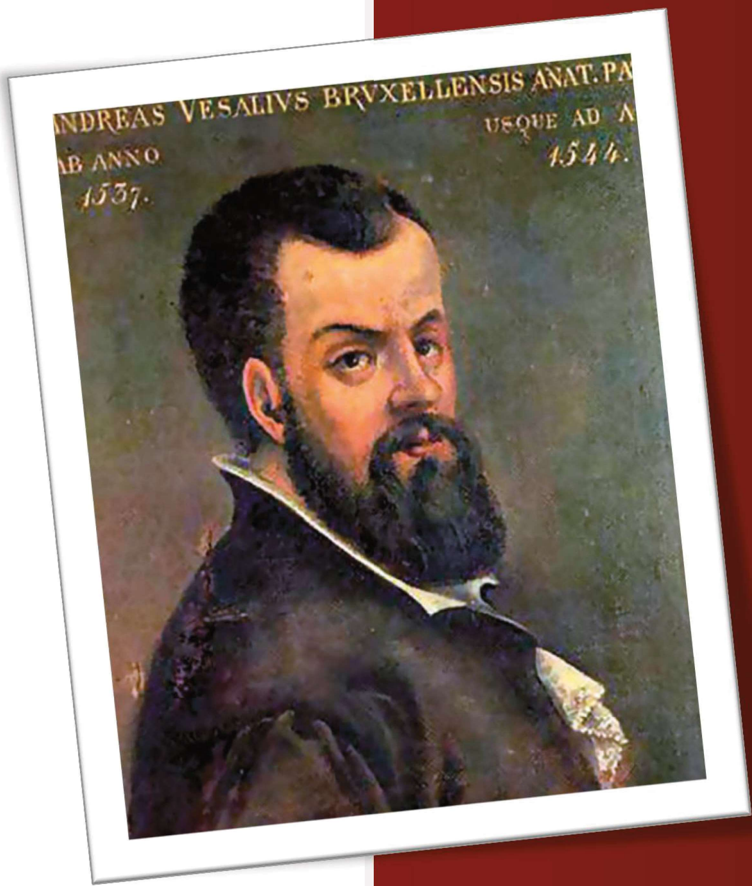

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Changes in the study of infectious diseases and epidemiology - from inflexible consensus to the acceptance of life-saving discoveries

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Summary: Over the decades, there have been many worldwide epidemics that have raised questions among researchers regarding their origin. While some scholars based their claims on scientific and evidence-based research, others based their claims on faith in gods and superstitions. During the 17th century, some researchers speculated that small creatures existed, causing an infection which brought about the diseases. However, due to the strong belief in the powers of the gods, it was difficult for researchers to progress and further develop this hypothesis. Puerperal fever is an endemic disease that was common among women giving birth. The mortality rate from this epidemic was extremely high. Over the years, many researchers tried to put an end to this epidemic and find a solution for it, but to no avail. Either they found what they thought was a solution that was implemented but did not produce any results, or they found a good solution that over the years would be perceived as correct, but due to the lack of solid evidence and an explanation, and due to a sense of insult on the part of those concerned, this solution did not produce an outcome.In 1864 Louis Pasteur published his great collection of articles, after many years of research, proving the existence of airborne microorganisms. As a result, he founded, together with several of his followers, the studies in microbiology, which is the basis of bacteriology.Due to Louis Pasteur's great contribution to our knowledge, drugs, anesthetics, and various hygiene tools have been developed that have significantly reduced morbidity and mortality due to epidemics worldwide.This article describes, through the presentation of the changes in the study of epidemiology, how fixation of thought, the lack of openness to research findings and the megalomania constitute a stumbling block in the pathway of science in general and the medical world in particular.

Résumé: Pendant des décennies , il ya eu partout au monde des épidémies qui ont amené maints chercheurs à examiner leur cause et origine. Certains ont porté leur jugement sur des études scientifiques et des recherches basées sur des preuves, d'autres se sont orientés vers des sources venant de dieux ou de superstitions. C'est pendant le XVIIième sècle que certains investigateurs ont spéculé que de petits organismes pouvaient être à l'origine d'une infection, qui serait la cause d'une maladie. Cependant, vu leur croyance en des dieux tout-puissants , il était très difficile pour ces chercheurs de progresser et de formuler de nouvelles hypothèses.

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La fièvre puerpérale a été pendant longtemps une maladie endémique parmi les femmes en accouchement. La mortalité était exorbitante. Pendant de longues années des chercheurs ont en vain taché de trouver une solution. Ou bien leur solution restait sans résultat, ou bien leur solution s'avérait exacte mais n'était pas praticable car non fondée sur des preuves ou trop à l'encontre des idées préconcues.

En 1864 Louis Pasteur publiait un grand nombre d'articles prouvant l'existence de microrganismes transmis par l'air. C'était le début des études en microbiologie, devenue par après la bactériologie. Suite à ces études de Pasteur, des médicaments, des anesthésiques et maintes techniques d'hygiène ont réduit sensiblement la morbidité et la mortalité dues aux épidémies de par le monde. Cet article montre, par la présentation des changements dans les études épidémiologiques, comment des pensées bornées et préconcues, un manque d'ouverture envers des résultats obtenus par des recherches, ou encore la mégalomanie ont constitué un blockage étonnant sur le parcours de la science et du monde médical en particulier.

Key-words: History of Medicine; Epidemiology; Louis Pasteur; Alexander Fleming; Ignaz Semmelweis; Childbed fever; Puerperal fever.

Mots-clés: Medical history; Epidemiology; Louis Pasteur; Alexander Fleming; Ignaz Semmelweis; Fièvre puerpérale.

The research of infection and the changes in dealing with it from a historical perspective

Throughout history, the world has known countless epidemics that killed many of its inhabitants. These epidemics raised many thoughts and ponderings among their researchers to explain the reason for these epidemics. Some tried to explain this by claiming that these were the acts of the gods, some claimed that this was witchcraft caused by humans, and some offered other claims that were rejected out of hand. Sometimes these claims have been proven over the years to be correct, but at the time of the ancient, claims that did not consider the presence of the gods, their existence and their actions that are found in all, were acknowledged as heresy and baseless claims.

Even in ancient times, several factors were recognized to contribute to the spread of diseases, and the foundation stones for their prevention were laid. The laws of impurity and purity (Tumah and Taharah) that exist in the Torah of Israel reflect correct knowledge and understanding of how epidemics spread, and the problems associated with them. Nevertheless, epidemics were mostly interpreted as divine retribution for human sins.

The Philistine plague and their reaction to it are described in the book of Samuel (1 Samuel, Chapters 4-6), and the demise of the Sennacherib armies before the walls of Jerusalem (2 Kings, Chapter 19 / Isaiah chapter 37) are classic examples of these thoughts. In the ancient literature of the Greeks and Romans and even in the Middle Ages and beyond, the epidemics were defined as the triumph of the dark forces and their causes as 'miasmas', that is, evil spirits rising from the marshes (We can see the progress in understanding that the swamps are a cause of disease since there is infection within them).[1,2]

Previous epidemics included other 'plagues' such as the Athens plague (described by Thucydides); the Antonine plague (smallpox – described by Galen); the Cyprian plague (described by bishop Cyprianus); the Justinian plague (a real Yersina pestis plague) and the great plague (caused by Yersinia Pestis) that broke in the 14th century; all are interesting testimonies for historical perspective of diseases by humans. In the Old Testament (Exodus, chapter 9, verse 15), the great plague is mentioned as the fifth plague brought by the Holy One and inflicted on the Egyptians. Some also claim that the plague that affected the Philistines (1 Samuel 5: 6) was also the great plague.
In the course of the 14th century, an epidemic of plague spread throughout Europe, killing about 75-100 million people, about half of the population in Europe at that time[3]. The outbreak of the plague was called "the black death" due to the morbid nature of black color in cultural perception, and due to the signs of the disease, which were characterized by black spots appearing on the skin of infected people with the disease. In this outbreak death rates of infected patients were nearly 100 percent.

Researchers believe[4] that the first Europeans infected with the disease were Italian merchants who embarked from Caffa (nowadays Feodosia, located in the Crimea peninsula) and reached the port of Genoa. Before their departure from Caffa, the city was besieged by the Tatars. During the siege, the plague broke out among the Tatars. The Tatars would throw the cadavers of the dead across the walls into the city of Caffa. Thus, many were infected without knowing. After the siege was lifted, the merchants returned to their country, Italy. The apparently healthy traders carried the deadly bacteria and spread the bacteria all over Italy. This is the description of monk Michele de Piazza as he wrote in his book "*The History of Sicily from 1337 to 1361*"[5]:
"*On the first days of October 1347, twelve sailboats from Genoa arrived at Messina port, as they escaped from the wrath of God for their evil deeds. The sailors brought such a violent disease in their bones that anyone who had a word with them was infected and could not save himself from death. Those who contracted the disease as a result of the respiratory infection suffered pain throughout their bodies and felt terrible exhaustion. Then a pus pustule the size of lens appeared on the thigh or arm. From it, the infection penetrated the body, and severe bloody vomiting began. This continued for three days, and death was inevitable.*"
As a result, the merchant's ships were expelled of the harbor, but the infection remained and killed many of Italy's population.
The first to attempt to interpret the concept of infection was Girolamo Fracastoro (1476-1553), an Italian physician and poet who lived in the 15th and 16th centuries. He expressed his opinion only as a hypothesis, deprived of any scientific basis, stating that small particles that can self-reproduce pass on from the body of the ailing onto the body of the infected [6,7].
Towards the middle of the 15th century, an epidemic spread in England, which moved very quickly to the city of Calais in France and into Europe until it reached Vienna. This epidemic is known as 'English sweat sickness.' The first outbreak of the disease

took place among the victorious forces of Henry VII after the Battle of Bosworth Field in 1485 and quickly spread, infecting the young and heroic soldiers[8]. John Caius (1510-1573), president of the Royal College of Medicine in London, wrote a report on the disease in 1552 [9,10], which was the first English essay that dealt with any specific disease. The disease remained unidentified; the hypothesis was that it might be a form of extinct microorganism.

Major trends in infection theory and bacteriology

For many years, physicians were the only obstetricians. At the end of the Middle Ages, when the first official hospitals were established, the midwives were also brought into some of the delivery rooms, and their job was to deliver the babies. In those years, Puerperal Fever casted a great fear in the mothers in the wake of the high mortality rates among the women giving birth.
In 1773, Charles White (1728-1813)[11], a physician from Manchester, England, published an article showing that the incidence of Puerperal Fever could be greatly reduced by isolating women with the disease. His article led to a significant decrease in the percentage of sick women, but when the method of isolating the sick quickly ceased, the percentage of morbidity and mortality, as a result, increased immeasurably. In 1795, Alexander Gordon (1752-1799)[12], a physician from Scotland, wrote that he accidentally caused the spread of the puerperal fever disease among some women and even caused their death.
In 1843, Oliver Wendell Holmes (1809-1894)[13] published his article "*The contagiousness of puerperal fever*" in The New England Quarterly Journal of Medicine, in which he researched the topic thoroughly and clearly showed how he could predict in advance which women would get puerperal fever after their birth and would even die, depending on the medical person, who would come into contact with them. And so, he says:

> "*The disease is so contagious that it is transmitted mostly from patient to patient by doctors and nurses... I reached this conclusion about the matter, with such accuracy that I could predict with my eyes which women would fall ill or not, which I did by learning about their assigned doctor or nurse. In almost all cases, my predictions turned out to be precise*."

Some argue that Holmes explained the relationship between a stay in the morgue before birth and mortality due to birth fever by "*physicians pass some of the dead spirits to their patients*." But whether he said it or not, Holmes claimed in his article: "*Puerperal fever is transmitted from one person to another, directly and indirectly*." Holmes also published in his article suggested instructions for physicians that are arriving from the morgue and wrote:

1. "*A physician who plans to take care of peripartum women is not allowed to take an active part in the autopsy of a woman who died from puerperal fever.*
2. *If a physician has participated in such an autopsy, he must wash himself thoroughly, replace every part of his clothing, and refrain from 24-hour care of*

the peripartum women. This is also the case in the case of autopsies whose suspected cause of death was simpler infections in the peritoneum.

3. *The same degree of caution should be evoked after the treatment of Erysipelas (skin rash) if it is necessary that the same physician should also treat the mother.*
4. *When a physician has treated even a single case of puerperal fever, he or she must carefully consider whether or not to treat another peripartum woman, and it is best not to treat women giving birth weeks since he has treated the fever, as it may contaminate the mother. It is his duty to act with the utmost caution in order to reduce the risk that a woman will become mortally ill.*
5. *If for a short period of time, two episodes of puerperal fever occur under the care of the same physician, he will be wise to halt his work for about a month until he is clean from the illness.*
6. *The occurrence of three or more cases of puerperal fever under the care of a single physician without additional events among the physicians around him is a clear sign that he is transmitting the disease.*
7. *Whatever the cause of these ignorant people who triggered so much suffering, it is time to recognize the possibility of a private epidemic being spread by a single physician and to recognize it not as an accident but as a crime; and in recognizing these events, the caregiver's duties to his profession should be swapped for his primary duties towards society".*

Despite all this, Holmes's remarks did not receive much attention, and physicians continued to deliver babies after post-mortem autopsies and mortality among the women giving birth continued to soar.

In 1847, Dr. Ignaz Semmelweis (1818-1865, whose birth year was recently celebrated by the scientific community[14]), published an article on the topic*: "The obstetrician cleanliness during labor"*.[18] Semmelweis, who published his article without knowing about Holmes's work, wrote that the physicians at the clinic where he worked would dissect the cadavers of women who died from puerperal fever and then moved to care for the women giving birth without washing their hands and changing their clothes. He claimed that the doctor was transferring rotting material from his body to the woman in his hands and clothes, so Semmelweis demanded physicians to wash their hands with chlorine. Semmelweis proved that this resulted in a significant reduction in deaths due to puerperal fever[15]. In his work, Semmelweis also claimed that puerperal fever is transmitted even by dirty bandages and used bedding.

While the director of Semmelweis's ward, Dr. Klein, was absent from the ward, Semmelweis placed bowls at the entrance to the ward and demanded that all physicians and students should wash their hands well before they went to care for the peripartum women. The students rebelled against this demand and felt that they had been stripped of their dignity and compared to midwives, who were required to clean their hands every day and present them for inspection. Although in the nearby hospital, under the direction of Dr. Bartsch, where only the midwives came into contact with the mothers, the mortality rate was far lower, the students refused to accept that this percentage was the result of the demand to wash their hands and protested against Semmelweis's demands.

About a year after the publication of Semmelweis's article, his friend, professor of forensic medicine by the name of Kolletschka, died prematurely. Kolletschka was wounded by a surgical knife during an autopsy. The next day, Kolletschka suffered severe headaches, and soon died. In the post-mortem examination, pleurisy, pericarditis, peritonitis, meningitis, and several more findings were found. This description reminded Semmelweis of similar autopsy reports of women who had contracted puerperal fever, and he said:

"*This is exactly the same image I saw in hundreds of women who died from the puerperal fever... Day and night I was haunted by the image of Kolletschka's disease, and I became more and more convinced of the similarity between the disease from which Kolletschka died and the disease I knew well, that slew so many peripartum women. The fingers of the students are contaminated from the autopsies and carry death crumbs from cadavers, they transfer them to the genitals of the woman at labor, especially to the cervix*."

The clear observation that Semmelweis had made did not persuade Klein, director of the department, when he returned to work. He resented the stupid and pointless guidelines of Semmelweis and removed them. The next day Semmelweis was fired, but he continued to argue that: "*Puerperal fever is the poisoning of blood by toxins that are created in the cadaver, and when they enter the organism, it is condemned to death. The toxins enter the woman's body from the doctor who examines her, or the students whose hands are contaminated from an autopsy, insert the toxins into the woman's genitals*[16]".
Only two physicians agreed to listen to Semmelweis's arguments, and with their help, Semmelweis was employed at the maternity ward at Bartsch's hospital. After promoting washing hands with calcium chloride in the hospital, mortality dropped to almost zero (Figure 1), but jealousy and superstition still dominated several physicians, who incited rebellion among the whole hospital staff against Semmelweis. In 1849 Semmelweis was dismissed again but did not surrender his struggle and expressed his anger in the letters he sent to physicians and the press.

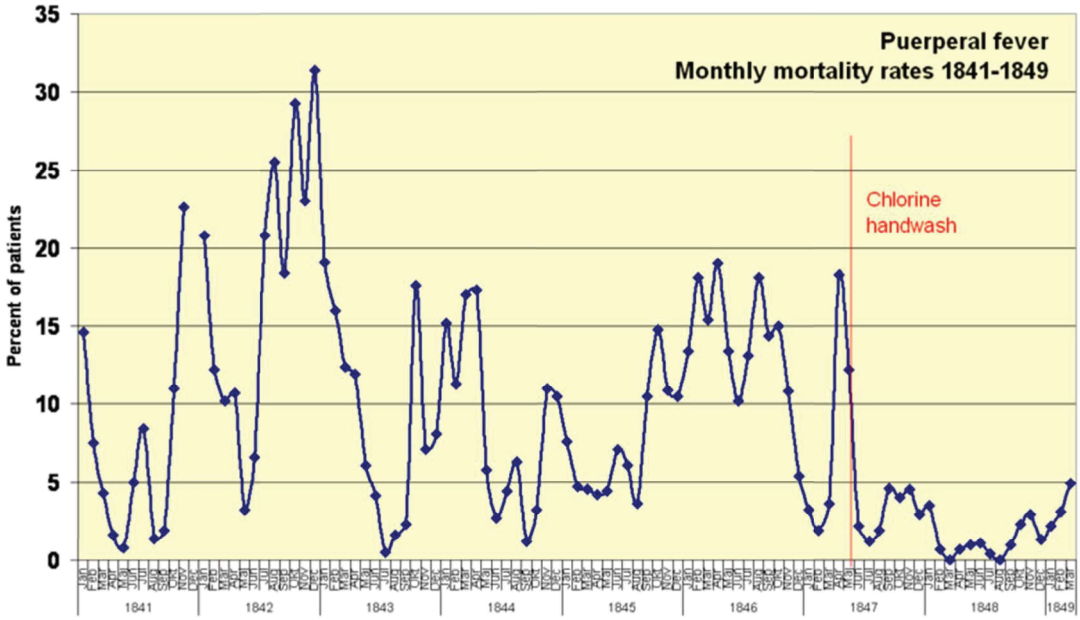

Fig. 1 Rates of monthly mortality among women in the clinic at the Vienna General Hospital between 1841 and 1849 as reported by Semmelweis. He invented and instituted a policy of disinfecting hands with chlorine until mid-May 1847. His work was terminated in March 1849

When Rudolf Virchow (1821-1902), the great German pathologist who laid the foundations for modern pathology, dismissed Semmelweis's theories and claimed that puerperal fever epidemics were related to changes in weather[64] (We can see the start of insight that the infection is airborne), Semmelweis reacted angrily and responded : "*Even the midwives would mock Virchow if he lectured them about the purpureal fever epidemics*".
In 1860, Semmelweis published a book called "*The Etiology, Perception, and Prevention of puerperal Fever*". In the first part of the book, Semmelweis presented statistics, charts, and tables of observations on which he grounded his theory. In the second part of the book, Semmelweis angrily spoke out against his opponents. In 1865, he got hospitalized in a mental hospital. After a short time, he died of an infection in his finger that spread to his arm, causing sepsis and eventually his death.

Louis Pasteur (1822-1895) started his higher education at the age of 16 and was admitted to the school of education at the then acknowledged École Normale University in Paris. After several months, and with intense longing for his home, which put him on the brink of a severe mental crisis, his father took him home. Four years later Pasteur was again admitted to the École Polytechnique, an acknowledged university, where he received his first degree in science, and a few years later acquired another degree in Crystallography (a branch of chemistry that studies the theory of crystals). Throughout his life, Pasteur debated many philosophical questions.
At those times, the wine industry suffered severe losses due to a disorder of the fermentation process. In 1857, as a result, several wine industry representatives approached Pasteur and asked for his assistance in solving their problems. At first, Pasteur noticed that some bacterium was involved in effective fermentation and that

in cases of poor fermentation another bacterium was involved[18]. Pasteur's hypothesis was a major shift in thinking because until then, fermentation was thought of as a chemical process that does not involve the activity of a living organism. Later in his research, Pasteur presented the notion that there are two forms of living organisms, one that needs oxygen to exist, and another which does not need such oxygen. Later, Pasteur contradicted the then prevailing opinion of spontaneous creation. Even so, there were still a few people who believed in spontaneous creation. After Pasteur's studies and hypotheses, the interest in this branch of research on bacteria increased. Many researchers were also swept by the idea, founding the new science of bacteriology.

In 1865 Joseph Lister (1827-1912), an English surgeon, used Pasteur's articles to understand that there were bacteria in the air that infected things that touched them and caused decay and rot. He invented and introduced to his own workplace, the hospital, the disinfection method, consequently significantly reducing the mortality and morbidity rates after surgery. Pasteur did not stop with the teachings of bacteriology and the rejection of the idea of spontaneous creation and continued to express his views on the infection theory. So, his student Roux recalls:
"*One day, when a discussion about the puerperal fever was being held at the Medical Academy, a well-known physician whose words got wide acclaim, spoke enthusiastically and offered reasons for the causes of puerperal fever epidemics in the maternity wards. Pasteur interrupted him immediately: "This is not the case with the epidemics in the maternity wards. The physician and his team transfer the bacteria from a sick woman to a healthy woman. When the known physician replied sarcastically that he was fearful that these bacteria would never be found, Pasteur hurried up to the board, drawing round organisms arranged in a chain. "You will see, this is its shape", he said*".

A few years later, in 1879, Pasteur and his colleague Dr. Paltz published their findings on puerperal fever. The results of their experiments were described, as they took blood from a woman who died of puerperal fever, and blood that contained spores of the bacteria that caused her illness and injected them into swine. In 14 days, the swine had died, and they concluded that the physicians contaminated with bacteria found in the cadavers of the women who died from puerperal fever were the ones who passed the bacteria and infected the peripartum women.

The contemporary and historical implications of the discovery of infection and the theory of bacteriology

Pasteur's discoveries were a major breakthrough for science and set a new course for the world of medicine[19]. From that point, scientists and researchers could have been able to focus their research in a more thorough, essential manner that started with the study of microorganisms associated with infections.
Inoculation and exposure to different tissues or materials from infected or sick people was a practice known to humanity long before Pasteur's discovery[20]. In 1715 Lady Mary Wortley Montague was infected with smallpox, causing wide esthetic damage to her face, just as occurred with her brother, who died due to the infection. In 1717,

her husband was assigned as an ambassador to the Ottoman court, Sublime Porte. Lady Montague was impressed by the Ottoman court knowledge and procedure of inoculation from smallpox. She had her son inoculated, and upon their return to England, the knowledge began to spread. Charles Maitland, who served in Istanbul with the Montague family as the embassy physician, granted permission to perform an experiment involving inmates and the inoculation to smallpox. His research showed a significant successful result, and the inmates were immune to smallpox after inoculation. The procedure finally gained public acknowledgment and publicity after the inoculation of the daughters of the prince of Wales in 1722[21].
In 1796, Edward Jenner (1749-1823), a physician in surgery and bacteriology, published[22,23] his writings on his invention, the vaccine. Edward Jenner invented the vaccine based on observations that the contents of a boil found in the body of a cow are 'vaccinating' those who touched it. On these grounds, he invented the first vaccine for smallpox, which included the injection of the contents of a boil from an infected cow onto a healthy human. Albeit, the profound understanding as to why the vaccine was beneficial, was only later revealed by Pasteur.

Following the perception that infection constitutes a factor in mortality among surgery patients, peripartum women, and other hospitalized patients, hospitals updated hygiene practices in the wards and areas of treatment. Rules were set to prohibit the transference of an instrument that came into contact with blood from patient to patient (for example, disposing of needles after one injection, which was innovative and never performed up until about 50 years ago); sterilization devices were installed to destroy the bacteria via heat (for the treatment of instruments that are used in multiple instances, such as metal surgical appliances); isolation rooms were constructed for patients with infectious diseases that may be airborne.

Over the years, Bacteriology is what guided Alexander Fleming, Nobel laureate in medicine, in his groundbreaking discovery of Penicillin. During World War I, Fleming served as a medical officer in the service of the British army for four years. During his military service Fleming encountered a large variety of bacterial infection victims, and he took this opportunity to continue his research on infection and the fight against it. After the war, Fleming returned to the university hospital where he had worked previously as a professor, doing both teaching and research. For all these years, Fleming had been interested in one thing, the discovery of the germicidal substances. He was curious about substances that could be effective in fighting bacteria without causing harm to healthy tissue. Most of the "anti-bacterial" substances developed by then had targeted all cells largely, causing patients no less harm than the infection itself.

In 1927, while working on one of his studies, examining the infection that caused the flu, Fleming noticed an interesting phenomenon: mold evolved in one of the mushroom plates containing a colony of bacteria, and around the mold, there was a bacteria-free ring. Fleming insisted on the importance of this accidental discovery and continued to study the properties of molds as a bactericidal agent. He discovered that a certain active substance inside the mold, which he called “penicillin”, could kill bacteria efficiently, even at a very low concentration. Next, Fleming went on to examine the effect of the new material on human cells to make sure it was non-toxic or harmful to the patient's body. When it became clear that penicillin was harmless to the living body, the way to develop an antimicrobial drug with unprecedented efficiency was paved.

In conclusion

This article portrays a historical perspective of infectious epidemiology. In-depth, the story that emerges through the scope of history presents an inflexible scientific consensus, a lack of openness to research and other opinions that led to the dwindling of research and scientific knowledge, and delayed understanding of many important mechanisms. Over the years, physicians began to heed to their colleagues, and so, despite the many years they missed, the stage was set for researchers and scientists to illuminate their work[24] and lead to the development of life-saving technologies and medications.

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