

Sample of penicillin mould presented by Alexander Fleming to Douglas Macleod, 1935.

The Surgical Legacy of World War II

Part 2: The Age of Antibiotics

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Author's Note: As our nation remembered the 75th anniversary of the battles of World War II back in December, we also should acknowledge the contributions of outstanding medical personnel – whose incredible vision, intensive planning and heroic efforts gave the wounded an extraordinary chance of survival. Among them are distinguished military surgeons, whose experiences inspired them to invent and implement methods and instruments we know the names of, because they are used every day in modern ORs. Yet there are countless names not mentioned here – men and women of all races, ranks and occupations, whose contributions are no less important to the effort to mitigate human suffering and who are profoundly worthy of being remembered. Why should we, as working CSTs, care about this increasingly distant history? Because the surgical technology profession can trace its inception to this period in American history – as the military planned for, and then entered – the first truly global conflict.

This series of articles provides an overview of the key surgical developments of World War II. The story began with “Part 1: Pearl Harbor, Preparation and Portability,” which was published in the December 2016 issue of The Surgical Technologist. Part 1 discussed the tactical and medical planning and build-up prior to America’s formal entry into the war following the attack on Pearl Harbor on December 7, 1941. That article

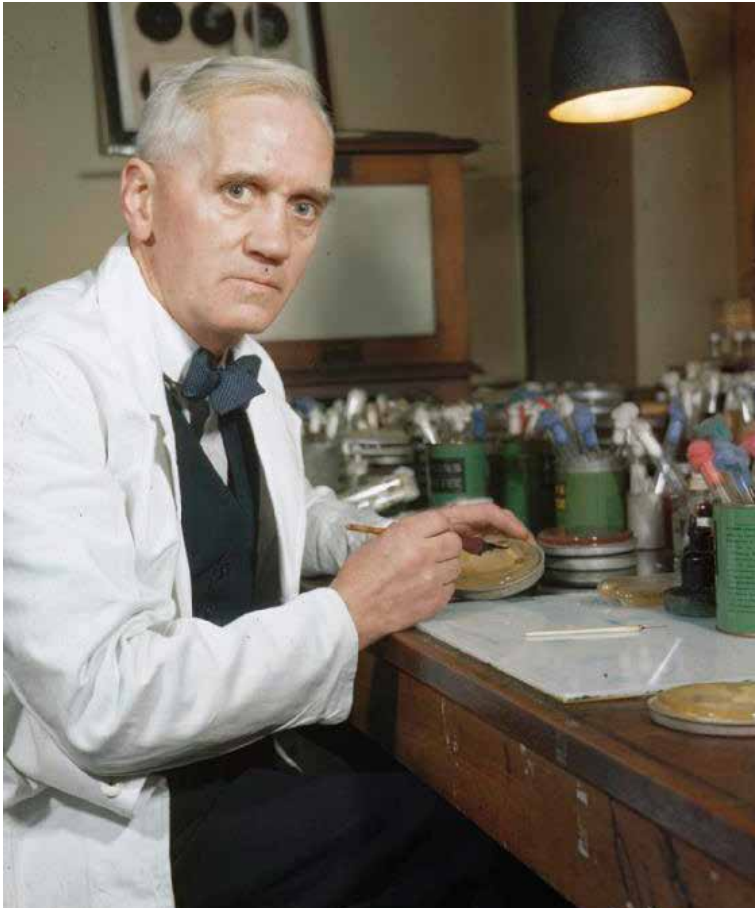


Soldiers of the 16th Infantry Regiment, wounded while storming Omaha Beach, wait by the chalk cliffs for evacuation to a field hospital for treatment, D-Day, June 6, 1944

Photo credit: US Army

LEARNING OBJECTIVES

- ▲ Learn about the scientists who discovered penicillin
- ▲ Recall when the drug first reached troops serving on the frontlines
- ▲ Evaluate how companies with fermentation expertise became critical to the process of creating the “miracle cure”
- ▲ Review what fruit became the saving grace in the road to producing penicillin to the masses
- ▲ Discuss how penicillin would come to alter decades of healthcare worldwide



Sir Alexander Fleming, who first discovered the mold *penicillium notatum*, is shown at his laboratory at St Mary's, Paddington, London. He was awarded the Nobel Prize in Physiology or Medicine in 1945 with Howard Florey and Ernst Chain.

Photo credit: Imperial War Museum

also summarized the logistical reality of delivering surgical care on the islands of the Pacific and the disparate terrain encountered around the Empire of Japan.

In this article, part 2, the focus will be on the development of penicillin and how the medical history of WWII would be remiss without it. The first use of penicillin occurred in 1942 as a direct result of the war effort in the US and Britain. Penicillin was immediately recognized for its value to society. By 1945, the scientific team that discovered and brought it to market were knighted in England and given the Noble Prize in Physiology or Medicine. To put this in context: this Nobel Prize was awarded less than six years after the discovery of medical dose capable penicillin. The discoverers of DNA waited almost 12 years before they received theirs. Penicillin is still widely touted as one of 20th century's most enduring breakthroughs, and its discovery has forever changed infection control in surgical practice.

THE WAR ON INFECTION

Infection and disease are historically greater causes of death among both military and civilian populations during war time than direct combat injuries. Early in WWII, both troops and civilian casualties were facing infections at an alarming rate. Pneumonia could race through barracks and ships before men ever reached the battle zone. Retained foreign bodies and dirt led to tetanus and devitalized tissue causing gangrene and septicemia. Osteomyelitis festered in compound fractures for numerous months after injury and often tragically resulted in delayed amputations – essentially the same medical response to these conditions before and during the US Civil War.

Many lessons were learned from World War I (1914-1918) and earlier conflicts regarding wound infections. The mortality rate and amputation rate for infected combat surgical sites took a staggering toll on veterans. After every conflict in our nation's history, amputees and grieving families were a part of most Americans' daily life. The impending war drove the quest for a better way to treat infection. The scientific community and fledgling pharmaceutical industry embraced the challenge as the nation prepared for the start of WWII.

When the war began, American GIs and corpsmen (precursors to CSTs in some cases) carried sulfanilamide packets and were trained to use it as a wound powder and oral tablet. It was quickly determined simply sprinkling a soil-filled gunshot wound with powder as a means of mitigating infection did not live up to expectations derived in a lab or hospital setting. The lack of available irrigation for these soiled wounds could not be curbed by the topical application of the sulfur drug. While the sulfa-based drugs reduced systemic infection to some degree when taken as a tablet, confidence in this drug therapy declined. Sulfanilamide's effectiveness was simply not greater than the risk of allergic reaction, toxicity and other serious adverse effects.

SERENDIPITY AND SCIENCE

Following WWI, Sir Alexander Fleming, a Scottish biologist, was already well known in the scientific community for identifying enzyme lysozyme (present in tears and mucous) and for naming and discovering the cause of gas gangrene, *c. perfringens*. Fleming and his British contem-



Medics attend to wounded soldiers on Utah Beach in France during the Allied Invasion of Europe on D-Day, June 6, 1944.

Photo credit: US Army



poraries relentlessly worked against the death rate caused by infection and infectious diseases. Fleming, and many others, spent so much time in hospital wards doing their research that he grew capable of determining types of infection simply from their characteristic smell. As Europe grew nervous for the impending second world war, these same bacteriologists were furiously researching infection control methods in an effort to avoid the calamity of WWI and the infected patients.

Fleming had discovered a bactericidal mold in 1928 upon his observation that a fungus in a forgotten petri dish seemed to repel a replicating *Staphylococcus* colony. Fleming immediately recognized the potential value of his discovery to the medical community. Converting a fungus into a medication, of course, is not an easy task. He and his team struggled with penicillin on two fronts: growing an adequate amount of the mold for experimentation, and determining how to identify and extract the elements of the

mold that killed the bacteria. Fleming and his early collaborators ultimately abandoned penicillin because they thought these problems were insurmountable. However, Fleming's mold discovery found fertile ground in 1938 when two scientists at Oxford read his decade-old research article. Ernst Chain and Howard Florey were inspired by the research, and thus began a mission to turn Fleming's fungus into an antibacterial medication.

Chain and Florey recruited a team of scientists to do the research and development on penicillin. The method of extraction was perfected in a single year in the primitive labs of Oxford. The development team recognized in studies of mice that parenteral administration was useless. Producing an injectable medicine was far more laborious, but ultimately successful. Urinary evidence of the drug and its desired bactericidal effect was present in the mice after injection. Research on the safety of the drug consisted of a few animal studies and a single, consenting, terminally ill

Snap Shot: The Discovery of the Placebo Effect

When medication supply ran short of the demand, medics improvised in order to relieve the suffering of the wounded soldiers. This practice did not go unnoticed. Colonel Henry K Beecher, MD, made the observation in 1943 that offering a severely wounded soldier a cigarette would reduce the amount of morphine needed to control pain. This would lead to Dr Beecher's discovery and research of the powerful placebo. The brain's ability to bypass pain pathways proved to be an act of humanity and a source of scientific inspiration. When utilizing placebos became a method to validate the action of a drug, Dr Beecher would come to question the morality of this practice and would soon be recognized as the father of medical ethics.

volunteer. No toxicity was observed, and the patient's blood and urine tested positive for penicillin and was found to kill bacteria. The scientists finally had the information needed to take their research efforts to the next level.

The first, true clinical trial of the therapeutic effect of penicillin occurred in London in February 1941. This second test patient had a raging staphylococcus infection on his face, one so severe that one eye had to be removed. The patient responded well and without toxic effect to the regimen of a penicillin injection given every three hours. To illustrate the challenges faced for mass producing the drug, the available supply of penicillin from the Oxford lab was not able to keep up with the amounts the trial demanded, and in fact that single patient and his infection, utilized all the available medicine. Supplies ran so low, that despite the demonstrable efficacy of this treatment, the patient died from sepsis when there were no more doses available. This challenge continued even into the beginnings of mass-production into 1942 when 50% of US supply was utilized to save a single patient.

The 1941 London trial continued slowly because of how difficult it was for the Oxford scientists to produce the penicillin. Supplies were so scarce that scientists and nurses collected the urine of the patients to study if it could be reprocessed to extract the medication. Penicillin quickly proved its effectiveness, but the Battle of Britain began to impact English manufacturing companies and their facilities, and the resources needed to develop and mass produce the drug were increasingly difficult to obtain.

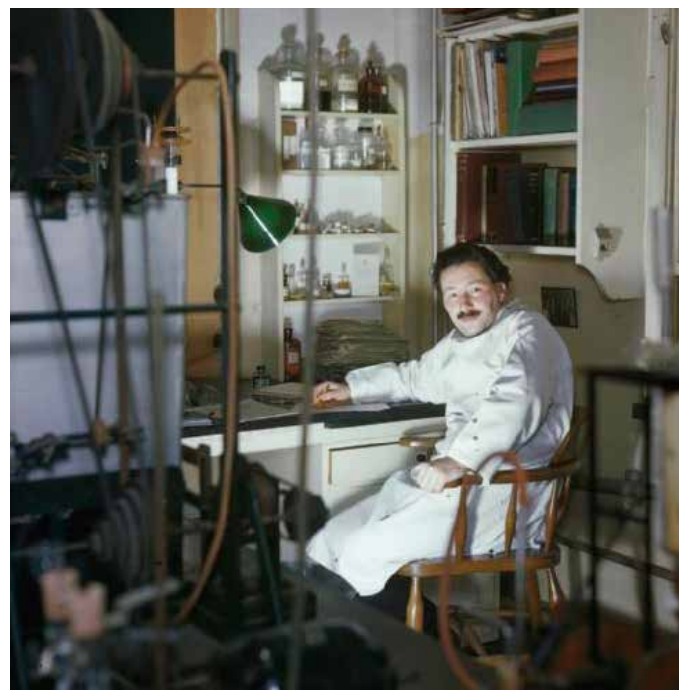
British scientists struggled greatly, as Fleming himself did, to grow the mold. Chain and Florey were desperate for help and looked to the US Department of Agriculture and a specialized research facility in Peoria, Illinois. The Peoria team was blessed with a serendipitous finding: an assistant presented the microbiologists a profusely moldy melon bought at a local market. The mold happened to be a relative of Fleming's penicillin and it possessed the same bactericidal properties as the original species.

The research and development team identified the best method for producing the finicky mold and subsequently issued a public challenge to help bring penicillin to market. Armed with ingenuity and abundant raw materials, the race to manufacture the world's "wonder drug" began. The companies with fermentation expertise, like Kentucky bourbon makers and established chemical manufacturers, quickly became the front runners in growing the finicky mold.



Professor Howard Florey makes notes as he sits at his desk at the Sir William Dunn School of Pathology in Oxford.

Photo credit: Imperial War Museum



One of the scientists involved in the search for a method of producing penicillin synthetically, Dr E B Chain of the Sir William Dunn School of Pathology at Oxford.

Photo credit: Imperial War Museum

"THANKS TO PENICILLIN, HE WILL COME HOME."

American drug manufacturers achieved remarkably quick success with the production process of penicillin. By May 1942, 400 billion units were available. Civilian use of the drug was strictly rationed so that most of this "miracle cure" could be reserved for the military. Penicillin first reached the troops in February of 1943 when the British and Americans were battling Italy and Germany in Sicily.

Production methods in late 1943 were advancing rapidly. American factories worked 24 hours a day in order to create the stockpile of penicillin that would accompany doctors during the invasion of Europe after June 6, 1944. Toward the end of the war, 21 American pharmaceutical companies were producing 650 billion units a month. The technological advances achieved during the search to increase penicillin production would catapult US pharmaceutical companies to enormous influence and success. These companies would grow to produce half of the world's pharmaceuticals by the late 1940s.

Originally, penicillin was seen by the US Army as the ideal drug to cure infectious diseases, such as venereal disease and respiratory illness. Soon, however, the effectiveness of penicillin at preventing infection was embraced wholeheartedly by the Surgical Consultants Division. Protocols for penicillin administration were determined and instructions for its use post-operatively were disseminated starting in mid-1944 until the end of the war. Penicillin is credited for saving thousands of lives at D-Day in the latter part of the war. One estimate suggests that the mortality rate was reduced 12% to 15% through the use of penicillin alone.

The Ongoing Battle Against "Superbugs"

Biologists are experts on evolution and adaptation. Alexander Fleming in his Noble Prize acceptance speech in 1945 cautioned the medical community to use penicillin judiciously to halt the impact of natural selection – the survival-of-the-fittest concept of evolution. Wide-spread, prophylactic use of penicillin and improper antibiotic use has brought the medical community into another costly war on infection with the rise of "superbugs." These resistant, adaptable bacteria are a true public health crisis for both patients and healthcare workers today. Surgical technologists are exposed to MRSA, VRE and other multiple resistant bacteria at increasing rates. Currently, research is being conducted on the necessity of routine pre-surgical antibiotics for different types of "clean" surgical cases.



A laboratory worker measures purified penicillin into ampoules or bottles in a laboratory in England in 1943. At the end of this process, a powder is left behind.

Photo credit: Richard Stone/Imperial War Museum

A laboratory worker checks on one of the 4,000 flasks containing corn steep medium and spores of penicillium mould in England in 1943.

Photo credit: Imperial War Museum



The Drug Companies of Nazi Germany

American pharmaceutical companies were full of German influence during the 1940s. German-born scientists and chemical engineers emigrated to the US after WWI and brought great advancements to the industry. The invention of numerous drugs from aspirin to meperidine (Demerol) can be credited to German intellectual prowess. Sulfanilamide, the first antibiotic used by the US in WWII, was developed in Germany in 1932.

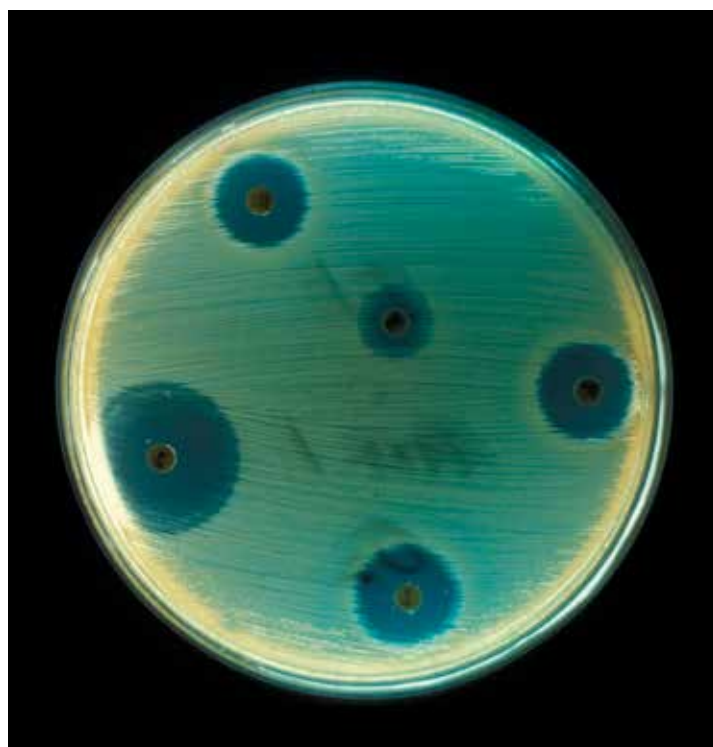
The successful mass-production of penicillin in the US is highlighted by the fact that the Germans could not accomplish this same task. Despite the fact that IG Farben, the German government's drug manufacturing parent organization, was at its height of industrial and economic power, it could never mass-produce penicillin for its own troops. The Nazi's even attempted to steal the original mold from Fleming's British laboratory. Penicillin remained unattainable for Germany, likely due to the lack of coordination between industries and agencies that the Americans excelled at. The Germans were desperate for penicillin for all the same reasons that the Allies were. Even though IG Farben had amassed immeasurable wealth through its expertise in the mass-production of so many other things such as truck tires (a reason Germany and other nations wanted to occupy the rubber tree-growing islands of the Pacific) and vitamin tablets, penicillin frustrated them.

Still, IG Farben was a significant source of funding for Hitler's regime. When Hitler's concentration camps became a source of human research subjects, IG Farben took part in horrific experiments on prisoners. The companies also produced massive amounts of chemical weapons. When the Allies won the war, IG Farben's participation in those atrocities would lead to its executives being convicted of war crimes at the Nuremberg Trials of 1947.

The task of injecting surgical patients with penicillin fell to nurses and corpsmen (surgical technicians). The historical account of Sgt James K Sunshine, an army corpsman/surgical technician, at a Normandy field hospital just after D-Day describes the role penicillin played in post-operative infection control.

"The Ward Tent: A quiet night. Sixty men fresh out of surgery are sleeping on canvas Army cots. I have drawn ward duty, and dutifully go from cot to cot with a syringe loaded with penicillin, thrusting it quickly into each man's buttock. It's a real wakeup call, but most of them are too sick to care."

The creators of penicillin were honored internationally with lavish award ceremonies and earning their faces on stamps and coins as well as earning the Nobel Prize. Yet, it was truly a collaborative effort among British and American scientists with the sacrifices of the US civilians on the homefront that led to one of the greatest victories of WWII. The collective efforts of these two nations not only produced a single drug, but opened a new frontier in the war on infectious disease. As American GIs fought across Europe and the Pacific, a new frontier of research into infection control was opened up by scientists at home. When 1.7



Modern antibiotics are tested using a method similar to Fleming's discovery.

Photo credit: CDC

million of them returned stateside for continued medical care of their war wounds, the hospitals were safer places to rehabilitate and receive restorative surgeries.

The next article in this series will cover the trailblazing doctors who discovered the surgical techniques that would alter the course of not only the veterans' recovery, but improve the human condition around the world.



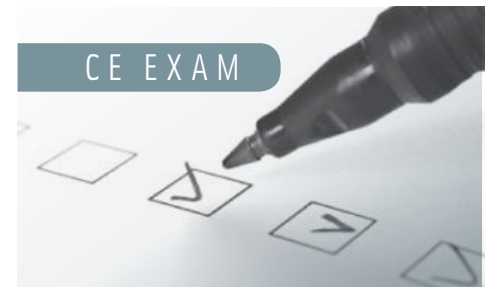
ABOUT THE AUTHOR

Dolores Goyette, CST, DC, is a member of the surgical technology faculty at Mass Bay Community College in Massachusetts, where she oversees clinical externships

in more than a dozen Boston area hospitals. The inspiration provided by stepping into some of the best hospitals in the country with her students fuels her passion for the study of surgical history, which has been driven by the military, the birthplace of the modern surgical technologist. Dolores is grateful for the support of her family and colleagues as she dedicates time to this research, and into writing this series of articles.

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The Surgical Legacy of World War II

Part 2: The Age of Antibiotics

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1. In what year did the troops first receive penicillin?
 - a. 1941
 - b. 1942
 - c. 1943
 - d. 1944
2. Sir Alexander Fleming first discovered a bactericidal mold in ____?
 - a. 1920
 - b. 1921
 - c. 1938
 - d. 1928
3. The first antibiotic used by the US in WWII, sulfanilamide, was developed in:
 - a. Australia
 - b. Britain
 - c. US
 - d. Germany
4. Ernst Chain and Howard Florey, inspired by Fleming's research, started a mission to turn fungus into medication in _____.
 - a. 1928
 - b. 1938
 - c. 1941
 - d. 1944
5. In 1942, ____ of the US supply of penicillin was used to save one patient.
 - a. 30%
 - b. 45%
 - c. 50%
 - d. 65%
6. An estimate suggests that mortality rate at the time of WWII was reduced by _____ due to the role penicillin played.
 - a. 10-12%
 - b. 12-14%
 - c. 12-15%
 - d. 10-15%
7. In 1943, Colonel Henry K Beecher, MD, discovered that (a) _____ would help reduce the amount of morphine needed for a wounded soldier.
 - a. Penicillin
 - b. Tourniquet
 - c. Alcohol
 - d. Cigarette
8. The scientific team of Fleming, Chain and Florey was knighted and awarded the Nobel Prize in ____?
 - a. 1942
 - b. 1945
 - c. 1950
 - d. 1947
9. What fruit was discovered to possess the mold relative to Fleming's penicillin?
 - a. Melon
 - b. Apples
 - c. Cantaloupe
 - d. Pineapple
10. In _____, Fleming cautioned the medical community to use penicillin judiciously to halt the impact of natural selection, an effect society is seeing in the rise of "superbugs."
 - a. 1941
 - b. 1945
 - c. 1947
 - d. 1949

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