The Best Shot

The Literary Club

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The year was 1950. I was six years old. If my memory serves me correctly, I was playing with some friends in a neighbor's back yard when I was bitten by an insect on my left cheek. I slapped my cheek, too late; and this was followed by immediate throbbing, burning pain. I ran home, holding back the tears, seeking my mother's comfort. She cradled me in her arms and applied a topical lotion. This seemed to ease the pain so I returned to play with my friends. Late that night, my cheek began to throb; I felt like my cheek was on fire. By 5 AM the following morning, the pain had intensified; I was running high fever. My face was apple-red and swollen; I could barely see out of my left eye. I was miserable. Mom retrieved one of those old glass mercury thermometers from her medicine cabinet and inserted it. My temperature approached one hundred and four. To this day, I will never forget the look of angst on her face; it reminded me of Edvard Munch's "The Scream"--- I told her, with all the confidence a 6 year old could muster, that I'd be fine.

Still in my pajamas, my mother drove me to our pediatrician; Dr. Wagner. He was legendary in Cincinnati; one of those old-time, tireless physicians who made house calls and who took care of 2 generations of Sterns. He told Mom I had cellulitis and if left unchecked would most certainly progress to rapid demise. And, like the kid on Norman Rockwell's Saturday Evening Post cover, I dropped my pants and received a shot of penicillin. At the time, I was too young to realize it, but a miracle had occurred. After a few more shots, my fever disappeared, my face assumed a normal appearance, and in 3 days I was back outdoors playing with my friends. Had the bite occurred in 1944, the year I was born, I almost certainly would have been history.

When my dad was a young boy he started a collection of U.S. Presidential letters and signatures which became the subject of a Literary Club paper he gave on June 2, 1997. At the time of his death, he possessed letters, mostly hand written, by every president, from George Washington on. He spent countless hours with his collection and derived great pleasure in researching potential acquisitions and occasionally bidding for them at auctions. As an aside, Malcolm Forbes, a contemporary of Dad's, was a serious collector of presidential letters, and on those occasions when Forbes entered the bidding arena there was no contest. Forbes got whatever he wanted. When Dad acquired a letter, he made a point studying its content and he went on to write a 3-4 page essay about each of these great men including what the letter revealed about the President's character.

When I was a youngster, Dad encouraged me to become a collector. He explained that what I collected didn't matter, but promised that I would enjoy the many facets of the experience. During my early years, I had some unusual collections such as soap wrappers from hotels which my father acquired while travelling about the country as a shoe salesman, match covers, and cigar bands which were originally collected by my grandfather. I neatly displayed each of these collections in albums, which I treasured and proudly showed to my playmates. As I grew older' however, I recognized that none of these collections would be a lifelong pursuit and ultimately they would be relegated to the dustbin of my personal memoirs.

On my 16th birthday, my grandmother gave me an autographed picture of Alexander Fleming. She knew I wanted to become a doctor and told me that Fleming had changed the course of medical history. She encouraged me to learn as much as I cold about him and I soon learned that he was credited with discovering penicillin. Recalling the pleasure I derived from my childhood collections, I decided to begin a collection of signatures and letters consisting of scientists and inventors. Since then, I've acquired a modest collection; concentrating primarily on U.S. scientists such

as Thomas Edison, George Washington Carver, Eli Whitney, Orville Wright, Albert Einstein and Alexander Graham Bell.

As a result of my childhood life saving experience with penicillin and my ownership of Fleming's signature, it seemed like a natural for me to explore the development and use of this so called wonder drug. Penicillin had an incredible impact on curing previously untreatable bacterial infections; and some would argue that its use during the latter part of World War II positively swayed the course of the war for the Allies. I believe that the discovery and use of penicillin was every bit as important as the introduction of the Salk and Sabin vaccines a decade later.

Let me now go back in time and relate the fascinating story of the discovery of penicillin. In 1875, a British physicist named John Tyndall was trying to determine whether bacteria were evenly distributed in the atmosphere or whether they gathered in so called clouds. To answer this question, he placed open test tubes containing a culture medium throughout his laboratory. He discovered that some of the test tubes contained no bacteria and he appropriately concluded that bacteria are not uniformly distributed. In 1876, he reported an additional curious finding. Several of his test tubes were contaminated with an "exquisitely beautiful" mold, *Penicillium*. In these tubes, the multiplying bacteria died and fell to the bottom. Unfortunately, Tyndall did not appreciate the extraordinary significance of the anti- bacterial effect of the *penicillium* mold. A year later, Robert Koch, a brilliant German physician, discovered that bacteria caused disease.

Fast forward 50 years. It was not until the summer of 1928 that Alexander Fleming noted the antibacterial properties of the *penicillium* mold. The story of his discovery is fascinating particularly because there were so many coincidences.

Fleming, born in 1881, was the 7th of 8 children, and was raised on his father's farm in Scotland. He was short and slim, athletic, and was probably best known for penetrating blue eyes. Early on, he was regarded

as an excellent student who had the uncanny ability to effortlessly digest all his homework at the last minute and still manage to rank at the top of his class. At 14, he left Scotland and moved to London where he attended the prestigious Regent Street Polytechnic Institute. Unfortunately, at age 16, the cost of Fleming's education was such that he was forced to drop out of school and he took a menial position as a shipping clerk. It appeared as if a productive career was not in the cards. As fate would have it, a wealthy uncle died and left him 250 pounds; sufficient funding for him to apply to medical school. He aced the entrance exams and received a full scholarship in 1901. He graduated virtually at the top of his class, managed to participate in the debating club, rifle and water polo teams and passed the surgical exam allowing him to become a Fellow of the Royal College of Surgeons. He never practiced surgery and upon graduation, he became assistant director of the St. Mary's Hospital bacteriology department where he worked until his death in 1955. He was not an exciting man and in today's parlance might have been described as a nerd. He was shy, a boring lecturer, and he enjoyed administrative detail.

Fleming split his time between the bacteriology lab and clinical care where he developed a successful practice, and became one of England's leading authorities on the treatment of syphilis. Syphilis, at the turn of the century was incurable, and in its late stages led to advanced neurologic dysfunction, dementia, and even death. In 1910, a German scientist developed a chemotherapeutic agent, called Salvarsan, a combination of copper and arsenic to treat syphilis. Administration was tricky, but Fleming had steady hands, and on a weekly basis he gave the drug intravenously with a crude needle and syringe. Many of his patients were quite wealthy; such that he made enough money to afford a home in Chelsea as well as a second one in the country.

Now, back to the discovery of penicillin; a story of coincidence and serendipity.

The first coincidence was that Fleming's tiny lab happened to be one floor above a laboratory where an expert on molds was growing *Penicillin notatum*; which was the same mold that Tyndall had experimented with half a century earlier. At that time, there was no way to contain the penicillin spores and as a result penicillin spores could ascend the stairwell and elevator shaft to enter Fleming's lab where doors were frequently left open.

Over the years, Fleming was regarded an expert on the bacterium *Staphyloccus,* which can cause lethal infections. He grew these bacteria on an agar gel in Petri dishes, just as we do today. As the story has it, in the summer of 1928, he was leaving on a 2-week vacation and rather than place the staphylococci swabbed Petri dishes in the traditional incubator as he usually did, he placed the dishes on his laboratory bench, at room temperature. He knew the staphylococci would multiply much more slowly at room temperature yet because he would be on vacation for two weeks, there would be sufficient time for the staph to grow. When he returned from his vacation, he made what turned out to be a landmark observation……

There were circular areas on the Petri dishes where bacterial growth had been completely inhibited. He reasoned that penicillin mold from the lab below his had landed on the agar while the staphylococci bacteria were being plated. Fleming was determined to understand what was going on and decided to investigate further.

Had he plated the Petri dishes with bacteria resistant to penicillin, there would have been no growth inhibition by the mold.

Had the spores NOT accidentally landed on the agar medium from the get go, staphylococcal growth would not have been inhibited. Penicillin only inhibits growing bacteria.

Even more incredible is that staph bacteria proliferate slowly at room temperature and more rapidly at the higher temperature of an incubator. In contrast, the *penicillium* mold grows only at room temperature. Had Fleming

not gone on his 2-week vacation; he would have used the higher temperature incubator where the *penicillium* mold would **not** have survived.

Next, there had been a severe heat wave in London before he left on vacation resulting in the laboratory temperature being the same as that of an incubator. On the day that he swabbed the Petri dishes; however, the heat wave broke such that the reduced laboratory temperature could now support the growth of the *penicillium* mold. Had he left on vacation a day earlier, the *penicillium* spores would **not** have multiplied and there would only have been a luxurious growth of staphylococci.

Finally, Fleming was a good scientist and knew he was onto something. The circular clear or kill zone created by the mold, which was surrounded by swarms of bacteria, cried for an explanation.

Fleming made additional observations. First, the broth on which the mold grew emitted a substance that killed bacteria; he named it penicillin. Next, he wanted to know if the penicillin inhibited the growth of other bacteria and found that most so called gram-positive bacteria were inhibited but tuberculosis was not. What I find somewhat incredible, given the fact that he made his living treating syphilis, is that he never tested penicillin against the spirochete, the organism that causes syphilis. It was not until 15 years later, during World War II that penicillin was routinely used to treat our troops for venereal diseases.

Fleming formally presented these seminal observations to his colleagues in February 1929 at the Medical Research Club in London. Following his presentation, the chairman, Henry Dale, later commented [quote] “He was very shy, and excessively modest in his presentation. When he finished, he remained at the podium to answer questions; there were none, not even a polite query out of kindness.”

Fleming published his observations on two occasions but his publications drew little attention. In light of these remarkable findings, why did he abandon studying this remarkable mold?

Here are some of the reasons:

He never realized that bacterial infections in humans could be eradicated by the systemic administration of penicillin despite the fact that he used Salvarsan intravenously for the treatment of his patients with syphilis. Unfortunately, in the lab, he never injected experimental animals simultaneously with the antibiotic and bacteria; had he done so he would have discovered that the animals survived despite a lethal dose of bacteria.

Next, the director of his laboratory, Sir Almroth Wright, who dominated Fleming throughout his career stated and I quote "antibacterial drugs are a delusion."

Finally, Fleming spent most of his career studying an enzyme named lysozyme which was secreted from nasal secretions. This remained the central focus of his investigations as he thought this enzyme was where the money was.

The setting for the next chapter of the penicillin story is in Oxford. Fleming had set the stage with the discovery of penicillin, but not being a chemist, he was never able to extract and purify it.

Fortunately, Fleming's 1929 article did not go completely unnoticed. A bacteriologist named C.G. Paine obtained a sample of *Penicillium* mold from Fleming, extracted penicillin, and successively applied it topically to several eye infections. The outcome was dramatic. He communicated his findings to Howard Florey, a brilliant scientist and physician, who a decade later led the team which discovered the potency of penicillin in the treatment of human systemic infections.

Unfortunately, Florey, like Fleming, did not think of testing penicillin to treat systemic infections. A German, Gerhard Domagk, in 1935, is credited as one of the first individuals to recognize the efficacy of intravenously administered antibiotics. He discovered a class of antibiotics called the sulfonamides or sulfa drugs. Within a few years of his publication, several other investigators substantiated his findings. Imagine if Fleming had know

this; penicillin would have been used a decade sooner and what an impact this drug could have had on the early part of World War II.

Back to Howard Florey, the brilliant young Oxford physician- scientist, who was to led the team that extracted, purified, and ultimately mass produced penicillin. Florey grew up and received his medical degree in Adelaide, Australia and in medical school recognized that he wanted to spend his career as a researcher. Research facilities in Adelaide were insufficient to follow his dream so he applied and won a Rhodes scholarship to study physiology at Oxford. In short order his talent was recognized by several of England's leading scientists, including Charles Sherrington, a Nobel Laureate in neuroscience. In future years, Sherrington and other scientists went to bat for him; supporting not only his academic career but also facilitated desperately needed research grant support. Thirteen years after his arrival in England, and following a highly political selection process, he was appointed Chair of Pathology at Oxford University.

Florey's scientific interest was bacteriology and he quickly recognized that his Department would nowhere without a biochemist on his team. To that end, one of his first recruits was Ernest Chain who at the time was working at Cambridge. Chain was a brilliant Jewish biochemist who had fled Nazi Germany in 1933. He also had an unsettled personality, was full of himself, and prone to inappropriate outbursts. By happenstance, Chain read Fleming's 1929 article and he also came upon some of Fleming's mold that was being used at Oxford for other purposes. Chain approached Florey and requested permission to study the antibacterial properties of the penicillin mold. Unlike Fleming, who had been rebuked by his chief when he requested to study penicillin, Florey gave Chain the green light.

Research funding for the penicillin project and other projects was the bane of Florey's existence. It has been said that the key to science is ingenuity but its engine is money. How true. Because he was unable to garner substantive support from Oxford University or from the British Medical Research Council, the equivalent of our N.I.H, Florey turned to the

Rockefeller Foundation, which supported basic science research. He proposed studying the biochemical effects of penicillin on microorganisms. He received a grant for $5,000 that allowed the research project to be launched; a tribute to both the merit of the project and Florey's brilliance.

Other scientists for the penicillin project were quickly recruited. One was Norman Heatley, a timid Ph.D. biochemist and technical wizard who was hired as an assistant to Chain to design a method to more productively grow and extract the penicillin from the mold. Unfortunately, their personalities clashed at every level; Chain, demanded unquestioned obedience and he treated Heatley in a demeaning fashion. Florey could ill-afford to lose Heatley and he reassigned him as his personal assistant. Heatley immediately accepted. Nevertheless, Chain's ego and paranoia were a constant and disruptive force throughout the project.

Contrary to Fleming's initial speculation, Chain found that penicillin was not an enzyme that dissolved bacteria. Rather, it was a simple molecule which was very unstable and difficult to work with. Chain, who had a short fuse, became frustrated and almost gave up his quest to extract penicillin; however, his curiosity as to how to overcome the "instability problem" kept the project alive. He finally discovered that by adjusting the acidity and by freeze-drying the penicillin, he was able to create a brown powder that was not only stable but was twenty times more powerful than sulfa.

Through trial and error, Heatley, the PhD technician, optimized the penicillin fermentation broth and also built a Rube Goldberg-like extraction device both of which significantly increased the yield of penicillin.

Excitement and urgency was beginning to mount; so much so that the Oxford team started an experiment on a Saturday which in Britain was unheard of. At 11:00am on May 25, 1940, Florey injected 8 mice with a lethal dose of streptococci; an hour later 4 the mice were also injected with penicillin. Heatley lived in the lab for the next 24 hours monitoring mice activity and at 3:28am the following morning he wrote in his note pad that 3

controls had died and that the last control [quote] “moved about drunkenly, respirations became slower, animal twitched and died.” The four that received penicillin all survived. On Sunday, Florey, Chain, and Heatley convened in the lab for a prearranged meeting. All three realized the incredible significance of the findings and their responses fit their personalities: Heatley said little; Chain was excited; and Florey, for whom understatement was his mantra allegedly said: “It looks quite promising.” The experiment was subsequently repeated with the same results.….**the era of antibiotics had been launched.**

Ironically, on this same date, when the magic of penicillin appeared to offer salvation for those with heretofore lethal infections, the war in Europe was looking bleak for the Great Britain and the Allies. The Germans had the Allied troops pinned down at Dunkirk. Neville Chamberlin, former prime minister and Lord Halifax wanted to cut losses and surrender; Winston Churchill would have none of it and remarked to his War Cabinet: [quote] “If this long island story of ours is to end at last, let it end only when each of us lies choking in his own blood upon the ground”. He received a standing ovation.

A month and a half later, the bombing of Great Britain had begun. The scientists at Oxford became increasingly concerned that their research accomplishment would be destroyed or worse their data would fall into the hands of the Nazis. Under such conditions, if future research was to be carried on, they had to preserve the penicillin spores. Heatley proposed rubbing the spores into their lab coats where they would be camouflaged and could lie dormant for years to come.

As conditions in Great Britain deteriorated and the London Blitz intensified, the threat of Nazi occupation became a reality, Florey, with much anguish, evacuated his two small children to the United States where their custody was assumed by Dr. John Fulton, a Rhodes Scholar colleague of Florey’s and a professor of physiology at Yale.

In August 1940, the Oxford Group published their striking findings in the leading British scientific journal, *The Lancet.* Their 2 page manuscript, which was undoubtedly one of the most important of the 20th century, received little attention. Florey hoped that pharmaceutical companies would take note and see fit to provide precious research funding for the penicillin project. Much to his dismay, there was no interest.

The next big step was the intravenous administration of penicillin to a human being. This posed an ethical dilemma. To minimize the unnecessary expenditure of a human life from a fatal allergic reaction, Mrs. Elva Akers, a 50 year-old lady with terminal cancer willingly volunteered. After 2 hours she developed fever and chills which proved to be secondary to contaminants in the penicllin. In a second injection, the impurities were removed and she had no reaction. The team concluded that the purified form of penicillin could be safely administered.

A second patient, police constable Albert Alexander, was found on the septic ward of the Radcliffe Infirmary. He was dying from a severe strep and staph infection of his face. He readily volunteered to receive penicillin and early on he experienced dramatic improvement. The research team was elated. Unfortunately, the supply of penicillin was extremely limited. It was known that penicillin is excreted in the urine and to maximize its use the Constable's urine was biked daily a mile to the Oxford lab, where it was extracted from the urine and re-administered. Just when it appeared that Constable Alexander was out of the woods, the team ran out of penicillin and he expired. At this point, the problem was the production of penicillin; even a **small** amount proved to be a very complex process that required space, time and specialized culture hardware.

Meantime, Britain's major cities were being destroyed by the German Luftwaffe, basic resources were dwindling, and thousands of citizens were being killed every month. There was simply no possibility for government or industrial support for the production of penicillin. Florey was desperate and once again turned to the Rockefeller Foundation which had provided start

up funding a few years earlier. The Foundation came through and provided $6,000 for Florey and Heatley to travel to the U.S.to garner support from either the pharmaceutical industry or the government. Shortly after they arrived in New York, Florey gave an eloquent and compelling presentation to the leadership of the Rockefeller Foundation. The leadership was sold on the potential for penicillin and provided Florey with strategic advice on how to proceed and they opened doors to facilitate contacts within industry and the government. One such contact was Charles Thom, the world's expert on molds and fungi. He, in turn, directed them to the Northern Research Laboratory in Peoria, Illinois where a team of scientists, who were the leading experts on fermentation technology, were producing chemicals for industry. Florey received a warm welcome and was promised full support provided Heatley remain in Peoria to establish fermentation techniques specific to penicillin.

Meanwhile, Florey traveled throughout the United States, meeting with the pharmaceutical industry. Despite several rejections, cashing in the chips was not in the cards. In February, 1942, Merck and Squibb, sparked by a feeling of wartime patriotism, signed an agreement to share research and production information. Additionally, the U.S. government endorsed this collaboration and made industry exempt from anti-trust litigation. These companies and subsequently many others invested millions of dollars to develop techniques for mass-production which results in a jump in production from 21 billion units in 1943 to 6.8 trillion units in 1945. Manufacturing techniques improved such that penicillin which in the past had been made in one-liter flasks with less than a 1% yield was now produced in 10,000 gallon deep fermentation tanks at 80-90% yield.

A month later, Anne Miller, was admitted to the Yale New Haven Hospital. She was on death's doorstep dying from an overwhelming bacterial infection following a miscarriage. Her physician, Martin Dawson, knew of penicillin's therapeutic potential from some experiments he had done. He contacted John Fulton, the previously mentioned Yale professor of physiology, who was Florey's close friend and surrogate U.S parent for

Florey's two children. Fulton beseeched Florey to contact Merck, and was able to obtain a teaspoon of penicillin; half the entire U.S. supply. Intravenous treatment plus urinary extraction led to a full recovery. Anne Miller lived to the age of 90 and was arguably the first U.S. citizen whose life was spared by the wonder drug.

By August 1942, momentum was building on both sides of the Atlantic. The tipping point had nearly been reached. The *LondonTimes* published a compelling editorial, *Penicillium*, noting [quote] "its strong anti-bacterial powers" and encouraged the industrial production of penicillin "without delay." Curiously, no mention was made of the scientists who had discovered and developed penicillin for clinical use.

As an interesting aside, Sir Almroth Wright, chairman of the Bacteriology lab at St Mary's, who a decade earlier had prevented Fleming from pursuing further research on penicillin wrote the *London Times* a famous response letter in which he proclaimed that Fleming should be credited with the discovery of penicillin. NO mention was made of the contributions from the Oxford Team. Reporters flocked to St. Mary's to get the story. Three days later, a rather feeble response letter from Oxford was published in the *Times* noting that Florey's team was the first to separate penicillin and demonstrate its clinical applications. Florey, when questioned by reporters, was tight-lipped; he didn't want the public to make demands that could not be fulfilled. To this day, Fleming is the name associated the discovery and development of penicillin; Floury and his Oxford colleagues have always been in the shadows.

Meanwhile, there was mounting and incontrovertible evidence that penicillin could make a dramatic difference in the management of battle acquired infections. More of the antibiotic needed to be produced. With one exception, the British pharmaceutical companies were unwilling to get involved. Furthermore, the British government was concerned that if the antibiotic was manufactured in a single facility it potentially could be destroyed during a German air raid. What evolved was a "mom and pop"

industry where penicillin was produced in basement laboratories all over the country yielding enough of the antibiotic to treat all of the British and civilian infections during World War II.

It didn't take long for physicians to discover that penicillin was not only effective in the treatment of battle wounds, but it was very effective in the management of venereal diseases. Paul Brown, a hand surgeon recounted: [quote] "V.D. was rampant in Italy. I sent such patients to the 23rd General Hospital in Naples. Every 3 hours a bell would ring and the patients would get a shot. The shots hurt like hell. With gonorrhea it was 8 shots over 24 hours but for syphilis it was 56 shots in a week. It was there that it was first proven that penicillin could cure these diseases, one of the few positive things to come out of the war."

Andrew C. Ruoff, III beautifully sums up penicillin's impact on the battlefield:" without antibiotics, we needed the good Lord to do a lot of the work. There's just no way to compare treatment before and after antibiotics."

Recognition of the scientific contributions of the men who discovered penicillin came in a number of ways. In 1945 Fleming, Florey, and Chain all received the Nobel Prize. Fleming and Florey were knighted in 1965. Finally, Fleming received Britain's highest posthumous honor. He was buried in the crypt of St. Paul's Cathedral in London. Despite these awards and honors, Fleming was fond of reminding others that, and I quote: "I did not invent penicillin. Nature did that. I only discovered it by accident."

Unfortunately, penicillin, which changed the course of medical history, was administered indiscriminately and drug resistant organisms quickly emerged. Within 5 years of penicillin's first use, 50% of *Staph.* infections demonstrated resistance. By 1960, methacillin, with activity against penicillin resistant strains, was developed. By the 1980's, methacillin resistant organisms (known as MRSA) had emerged. Again industry responded with the development of effective new therapies. A

predictive pattern emerged: introduction of a novel antibiotic, emergence of resistant organisms, and an urgent need for the development of a new drug.

Today, the effectiveness of antibiotics in threatened on several fronts.

First, there is an ever increasing antibiotic resistance among many bacterial strains. Some physicians prescribe antibiotics indiscriminately and every time an antibiotic is administered, bacteria are working to change their genetic code to become resistant. Furthermore, 75% of all antibiotics used in this country are consumed in the agriculture industry. Antibiotics, for example, are routinely given to pigs to make their digestive system more effective and hence speed animal growth. The outcome is the production of more resistant strains.

Next, the world is running out of effective antibiotics. Between 1940 and 1962, more than 20 new classes of antibiotics were marketed. No novel classes of antibiotics were licensed in the seventies, eighties, and nineties and since 2000 only three new classes of antibiotics have been approved. In addition, 90% of antibiotics which are developed are not approved by the FDA.

Finally, there has been a dramatic reduction in the number of pharmaceutical manufacturers engaged in the R & D of antibiotics. Research is expensive and resistance develops quickly rendering a newly developed antibiotic out of date; and potentially having a negative impact on the bottom line.

Today, the threat to human life from microorganisms and viruses remains staggering. New bacteria will emerge with regularity and challenge society's monetary and intellectual capital. What the future holds is conjectural. Although I doubt the battle will ever be won, I'm hopeful that our government and the pharmaceutical industry will support our scientific community with research dollars in hopes of discovering cures just as Fleming and Florey and Chain did over seventy-five years ago.

THANK YOU