Economic Research Working Paper No. 26

Economics & Statistics Series

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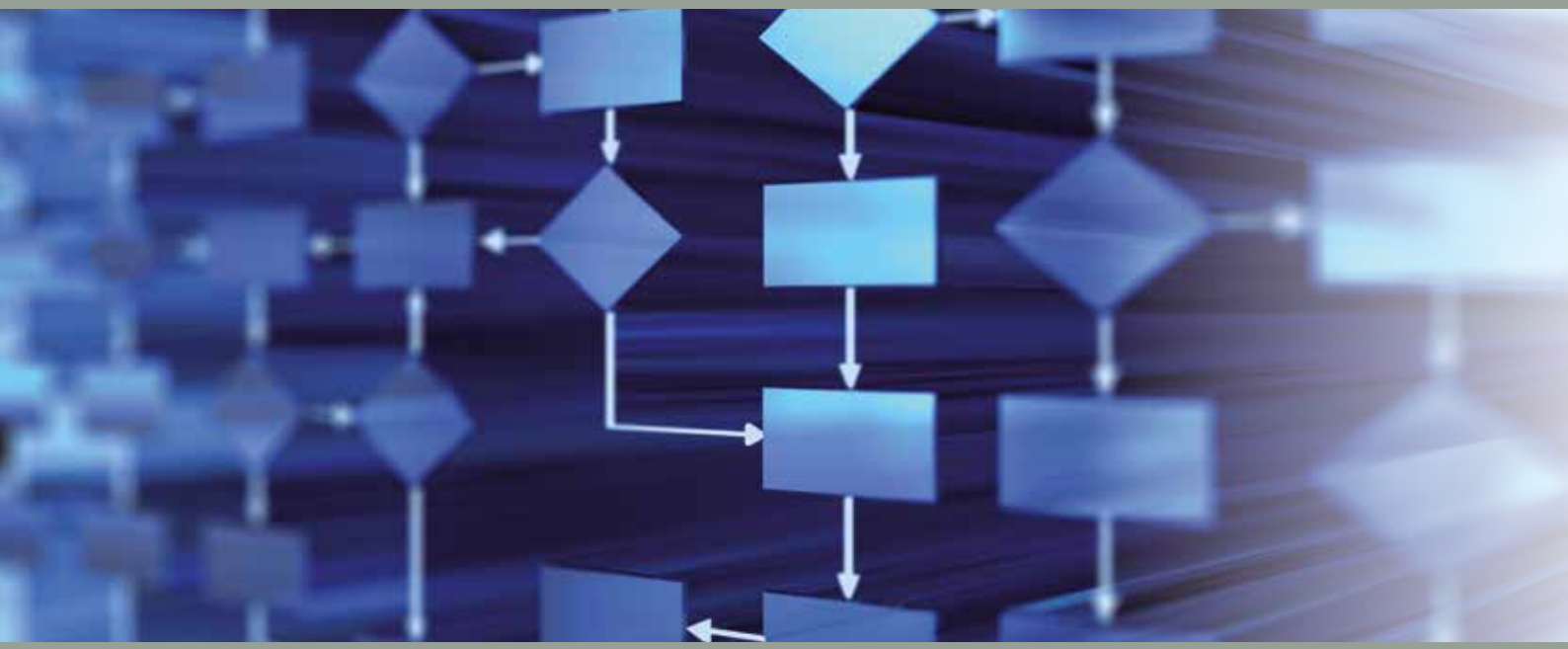
Bhaven N. Sampat



November 2015

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Intellectual Property Rights and Pharmaceuticals: The Case of Antibiotics

Bhaven N. Sampat*

Abstract

The development and diffusion of antibiotics contributed to large improvements in human health and living standards. The antibiotic revolution also spawned the modern pharmaceutical industry. This paper reviews the development of the early antibiotics, and the roles of intellectual property rights (in particular, patents) in their development and diffusion. Though today the pharmaceutical sector is typically characterized as one industry where patents are absolutely essential for innovation incentives, patent incentives had a subtle role in the early years of the antibiotic revolution. Indeed, in successive stages of the antibiotic revolution there was increasing focus of pharmaceutical firms on patents and exclusivity. The new technologies shaped patent laws and practices as much as patents influenced innovation incentives: technology and institutions co-evolved. Beyond patents and intellectual property, wartime exigencies and several forms of university-industry collaboration also appear to have been important in supporting breakthrough antibiotic innovations.

Keywords: Innovation; Research and Development; Technological Change; Intellectual Property Rights; Government, War, Law, International Relations, and Regulation; Health.

JEL Classification: O3, N4, I1

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The views expressed in this article are those of the authors and do not necessarily reflect the views of the World Intellectual Property Organization or its member states.

Acknowledgements

This paper was prepared as a background study for WIPO's *World Intellectual Property Report 2015 on Breakthrough Innovation and Economic Growth*. For helpful comments, thanks to participants at a WIPO workshop held in Geneva in February 2015, including Luigi Orsenigo, Roger Burt, David Mowery, and Nicola Searle.

* Columbia University and NBER

> In 1931, humans could fly across oceans and communicate instantaneously around the world. They studied quantum physics and practiced psychoanalysis, suffered mass advertising, got stuck in traffic jams, talked on the phone, erected skyscrapers, and worried about their weight. In Western nations people were cynical and ironic, greedy and thrill-happy, in love with movies and jazz, and enamored of all things new; they were, in most senses, thoroughly modern. But in at least one important way, they had advanced little more than prehistoric humans: They were almost helpless in the face of bacterial infection.
> *Thomas Hager, The Demon Under the Microscope. (2006).*

1- Introduction

This chapter examines the the development and diffusion of antibiotics, one of the handful of breakthrough inventions of the early twentieth century (Mokyr, 2000) that revolutionized health, clinical practice, and industry. Under the "big tent" definition of antibiotics, as any chemicals that have microbial properties, (Bentley and Bennett, 2003, Bentley, 2009), the three breakthrough antibiotics are sulfa drugs (developed in Germany in the 1930s), penicillin (developed in the United Kingdom in the 1930s, but first mass produced in the US later), and streptomycin (developed in the US in the 1940s). These breakthroughs also spawned a range of follow on innovations, including semi-synthetic penicillins, cephalosporins, and a range of broad spectrum antibiotics.

This chapter draws on historical accounts of these developments to try to assess the roles that patents had in the development and diffusion of these inventions, and how patents interacted with broader aspect of innovation systems. This turns out to be a difficult task. One well-known reason why assessing the impact of patents on innovation (and other outcomes) is challenging is that patent laws are related to many other factors shaping innovation, so it is difficult to say what roles patents are playing relative to other correlated factors. The histories presented here suggest an even more fundamental reason. Patent laws and patent strategies co-evolve with science and technology, market structure, and supporting institutions. As a result, the roles that patents had in the stories of the breakthrough antibiotics appears very different from the roles they had in the development of the various follow-on innovations. It also shows that beyond patents, wartime exigencies and several types of university-industry collaboration appear to have been important in supporting early breakthrough antibiotic innovations.

I proceed as follows. In Section 2, I discuss the clinical and economic benefits from the breakthrough antibiotics. In Section 3, I discuss their development and diffusion. In Section 4, I provide some data on the later evolution of the antibiotics sector, including market structure and patenting activity. Drawing on these discussions, in Section 5, I consider the roles that patents and other forms of intellectual property had in the development of the breakthrough drugs and other antibiotics. Section 6 concludes with a discussion the broader aspects of innovation system that were important in each antibiotic and a discussion of the roles of patents in pharmaceuticals more generally.

2- Antibiotics as Breakthrough Innovation

The discovery of antibiotics revolutionized human health. Jayachandaran *et al* (2010) find that sulfa drugs led to sharp decreases in mortality from a range of conditions (maternal mortality, pneumonia, scarlet fever) between 1937 and 1943. This increased overall life expectancy in the US between .4 and .8 years, between 8 and 16 percent of the total increase in life expectancy over this period. Cutler *et al*. (2006) argue that "sulfa and penicillin were the wonder drugs of their era" (13), showing that infectious disease mortality in the US fell sharply after their discovery respectively, achieving their current level by 1960. Achilladelis (1993) shows sharp drops from tuberculosis and pneumonia mortality globally after the antibiotic revolution.

There is some debate over the role of medicine versus other factors in this decline. The demographer Thomas McKeown (1976) famously noted that the decline in infectious disease mortality pre-dates antibiotics, and is due to other factors (improved income, nutrition, public health) as well. Preston (1975) disputes the primacy of income, but points to other public health interventions. But Cutler *et al* (2006), reviewing the entire body of evidence, suggest that post-1930 declines in industrialized countries were due largely to medical treatments, primarily antibiotics.

As with many new technologies, diffusion patterns were uneven. For example, Jayachandaran *et al* (2010) show that despite relatively rapid diffusion of sulfa drugs in the US- aided in part by low prices (more on this below) - they diffused more quickly to whites than blacks. Acemoglu and Johnson (2007) suggest that the diffusion of these drugs helped contribute to a global convergence in life expectancy.

The clinical value of antibiotics is unquestionable.[1] What about their economic effects? It is difficult to place an exact economic value on the benefits of new medical technologies, in general. The decline in mortality from infectious diseases in the first half of the twentieth century was large, as shown above. Nordhaus (2002) suggests that the value of improvements in life expectancy over this period is of the same order of magnitude as the welfare gains from per capita GDP growth over the first half of the twentieth century. We would expect similar orders of magnitude were the estimates collected globally, especially given the higher burden of infectious disease outside the US.

In addition to the value of improved life, health can also improve productivity. There is a broad literature (mostly, cross-country growth regressions) showing a strong relationship between disease and economic growth and development. It is difficult to estimate any causal relationship between the two, since third factors can affect both health and economic outcomes, and the relationship is potentially bidirectional. In one attempt to solve this problem, Acemoglu and Johnson (2007) examine how the global diffusion of antibiotics (and other medical interventions) affected life expectancy. They then use these estimates to examine the relationship between health and economic outcomes in an instrumental variables approach. They found that little evidence of the effect of improved health on economic growth per capita, in large part because the new technologies led to significant population increases. In a similar approach, using variation in diffusion of sulfa drugs, Bhalotra and

[1] There were also spillovers to other diseases: eventually, antibiotics also facilitated other forms of treatment for example of cancer and transplantation, and reduced infection from surgery, which allowed for medical progress in other disease areas as well (Le Fanu, 2011).

Venkataramani (2012) find that introduction of sulfa drugs in US improved schooling, income, and employment, which they suggest is a long-run effect of improved childhood health.

Beyond their impact on health, growth, and welfare (as we shall discuss in more detail later) the antibiotic revolution had broader effects on industry. Sulfa and the first wave of antibiotics, were the "magic bullets" that demonstrated the potential of medical progress. Le Fanu notes together with steroids, antibiotics were "the fuse that lit the chain reaction of post-war medical innovation" offering the ideas about the "possibilities of science were limitless and one day seemingly insoluble problems would be overcome" (Le Fanu, 2011, pp. 162-163). Temin (1980) and others suggest that the antibiotic revolution also changed the very structure of the drug industry, and patent laws and regulations governing it, as will also be discussed in more detail below.

3- The Antibiotic Revolution: Case Histories

Sulfa

Like penicillin that would follow it, the development of sulfa drugs was a response to tremendous toll that infections had on soldiers during World War I.[2] Streptococcal infections, in particular, were responsible for many fatalities on all sides during the War. These infections also had a large civilian burden: boils and rashes, infections of heart, lungs, throat, blood, spine, ear, childbed fever, scarlet fever, and rheumatic fever were common wartime afflictions (Hager, 2006). "Strep was responsible, they said, for half the white hairs on every physician head" (Hager, p. 106). The first effective treatments against streptococcal infections, the sulfonamides, also known as sulfa drugs, emerged from Germany after the War.

Since the late nineteenth century, German chemical companies had begun to develop competencies in producing coal tar, a byproduct of coal production that became an important source of new chemicals. Such byproducts were the basis for the synthetic dye industry. German firms such as Bayer, BASF, and Hoechst became international leaders by the turn of the century, partly reflecting strong university-industry linkages (Murmann 2003).[3] Economic disturbances during World War I led German firms and the government to search for new product lines. According to at least one historian, Bayer was hit particularly hard by the war, after appropriation of its patents and trademarks by Americans (Hager, 2006). There was a strong push for innovation and patents. According to Hager (2006): Bayer "needed new products, new patents, to replace the losses of war" (74) and the focus was on synthetic chemicals.

Earlier, in 1910, German chemist Paul Ehrlich had shown that compounds from dyes could be used to kill bacteria. Salvarsan, an arsenical compound marketed by Hoechst, became an important syphilis treatment. While it ended up being toxic (and eventually replaced by penicillin) it proved that synthetic chemicals could cure disease and generate revenue (Hager, 2006). This led other academic and industrial researchers to search for chemicals to treat infectious disease. There was particular excitement at Bayer about a family of azo dyes which had showed some success in

[2] This summary is based on the account in Hager (2006).
[3] A number of prominent Swiss chemical companies (Sandoz, Ciba, Geigy) also emerged out of the dyestuffs industry.

killing bacteria in test tubes (Hager, 2006, p. 130). The research effort involved attaching and removing specific atoms and molecules to the core dye structures.

One variation was created when the molecule sulfanilamide was attached to an azo dye. This azo plus sulfa combination was tested by Gerhard Domagk, director of Pathology and Bacteriology at Bayer, and found to have strong effects in curing streptococcal infections in mice. As Hager (2006) describes it: "As the Christmas holidays approached in 1932, Bayer was abuzz about the first drug to ever work against bacteria. After Domagk showed the Kl-730 results to Horlein, a series of meetings was set up with Bayer patent attorneys, marketing men, and higher administrators…A preliminary name for a new drug, Streptozon, was quickly approved" (Hager, 2006, p. 137).

Domagk and other scientists at Bayer not only started thinking about how to patent this compound, but also to search for and patent all related ones that worked: The original development became a platform for follow-on invention: "It became clear that Bayer chemists could make effective antistreptococcal medicines whenever they wanted by attaching sulfa to an azo dye in the right place" (Hager, 2006, p. 137). Accordingly, Bayer focused on rapidly testing and patenting the best. At that time Germany, like most other countries, did not allow product patents in pharmaceuticals. This law did not change until 1968 in Germany. In 1949, Britain allowed product patents, in 1978 Italy did, in 1967 France did (See Dutfield, 2009).

There was enthusiasm at Bayer about the drug: "It looked as if Streptozon was simply the first of what could be a series of azo-based antibacterials effective against all sorts of diseases. It looked as if Bayer has prospected its way into what could be an incredibly rich pharmaceutical field" (Hager, 2006, p. 143). However, the drug was discovered through trial-and-error learning, and there was no knowledge of how the azo structures actually worked, including how the "sulfa" turned on the azo dyes. As experiments continued, there were some results suggesting that sulfa even when attached to other molecules (beyond azo dyes) had a therapeutic effect, but this was either deliberately suppressed or (in view of the deep attachment to dyes at Bayer) ignored (Hager, 2006).

The initial testing and diffusion of Streptozon was local. Once the patents were filed in 1932 the drug was distributed more broadly, including to hospitals. The German patent for Streptozon, DE 607537 on "proceses for the production of azo compounds" (Lesch, 2006) was issued in 1935, and assigned to I.G. Farben, the German conglomerate which included Bayer and other German chemical companies. Following the issuance of the patent, Domagk published an article on the discovery and Bayer released the drug more broadly for further experimentation. Around the same time the drug was renamed Prontosil, reflecting information from Bayer tests that it was effective not just against streptococcal infections but others, including staphylococcal infections and gonorrhea, as well (Hager, 2006; Lesch, 2007). Soon after this publication, and case reports from German physicians who had been supplied the drug,, researchers worldwide became enthusiastic about the drug. Around the world, clinicians and researchers began doing laboratory and clinical testing on Prontosil using samples from Bayer (Hager, 2006; Lesch, 2007).

Diffusion to France was slower. Bayer was apparently apprehensive about providing samples to French researchers since they (like Indian drug companies today) had a reputation for and skill in reverse engineering drugs. When Horlein was approached for a sample by French medical chemist by Ernest Fourneau he was reluctant: "They both knew what the French scientists was likely to do when he got hold of the new

drug: study it, solve its structure, devise some new way to make it, then give it to French drugmakers who would compete with Bayer" (Hager, 2006, p. 164).

Though the lack of a product patent may have limited diffusion to France, the difficulty in obtaining supplies had an unintended effect. Based on the information in the patent document and other sources, Fourneau replicated approximate versions of Prontosil. He also found, through this tinkering process, that pure sulfanilamide (not linked to the azo dye) was responsible for the therapeutic effect. This fact, either ignored or suppressed by Bayer, had an important impact on diffusion: "Simple sulfanilamide, a colorless, common, unpatentable, off-the-shelf chemical used by the pound in the dye industry" was as effective as Prontosil. "From that moment on, the German chemists' patents had no more value whatsoever" (Hager, 2006, p. 170). This discovery opened up global investigation on sulfa, with scientists publishing widely, discovering new variants active against a range of infectious disease.

Even without patents, Bayer continued its efforts, using its first in class status, brand, and strong sales force to maintain competitive advantage. It also relied heavily on trademarks (Prontosil, Proylin, Prontablbin), and evidently made significant revenues from sulfa drugs. Soon sulfa had diffused broadly throughout Europe and the US. An experimental version of the Bayer drug saved President Franklin Delano Roosevelt's son (FDR Jr.) from a strep throat infection, fueling a surge in popularity in the US (Hager, 2006). There was broad prescribing: Hager notes "By the end of [1937] consumers could buy pure sulfa over the counter at their local drugstores under twenty-odd trade names" (Hager, 2006, p. 196).

There was also a growth of sulfa patenting in the US, which (unlike many other developed countries at the time) had pharmaceutical product patents. While pure sulfa not patentable, sulfa could attach to other molecules, and there was heavy patenting of variations. Despite many variations and use, there were still no large scale trials of sulfa in the US or anywhere else. A range of deaths linked to some of the sulfa drugs in the US contributed to the passage of the Food, Drug, and Cosmetics Act of 1938, which created the modern Food and Drug Administration with powers to regulate drug safety and efficacy (Temin, 1980). Among other things, the Act created the need for drugs to be prescribed by doctors (rather than sold over-the-counter), which would change marketing strategies of drug companies in the decades that followed. This helped shut down a lot of low-quality drug retailers, and spawned the search for safer and less toxic sufla variants (Temin, 1980). According to Bentley (2009) more than 5000 new sulfa drug variants were prepared by 1945, revolutionizing the treatment of the disease they treated. The main companies profiting from this sulfa revolution were chemical companies which had dyestuff experience, many of which were German and Swiss (Achilladelis, 1993).

Though the sulfa drugs had a tremendous impact on the treatment of bacterial infections – the first wonder drugs – they had toxicity issues and there was some concern about resistance. Roy Porter notes "They nevertheless represented a major step towards the control of bacterial diseases, and their development spurred research into other anti-microbial agents" (Achilladelis, 1993, p. 454).

Penicillin

Domagk won the Nobel Prize for Chemistry in 1939 for the discovery of sulfa.[4] Only six years later, Alexander Fleming, Ernst Chain, and Howard Florey would win prizes for discovery and development of penicillin. This discovery is among the most well documented in medical history. Here I draw mainly on the accounts in Wainwright (1990), Neushul (1993) and Kingston (2000).

Fleming's discovery of penicillin is one of the most cited examples of "serendipitous" discovery in science. As the story goes, Fleming laid out a dish of the bacteria *Staphylococcus* which became contaminated with a spore from what would later be identified as *Penicillium notatum*. Fleming surmised that the mold inhibited the growth of the bacteria. There is considerable disagreement on how surprised he was about this fact, and also about how the mold actually got onto the dish (Wainwright, 1990). Whatever the case, in 1929 he published a paper on the effects of penicillin, but this account did not emphasize clinical or medical utility or highlight potential medical uses.

According to Wainwright (1990), before Fleming, there had been conjecture that fungi could have activity against bacteria. Some previous scientists, including Joseph Lister, may also have speculated that varieties of penicillin may be medically useful. However, almost all of these previous explorations were unpublished, and nonspecific.

In the years that followed, Fleming and his colleagues at St. Mary's did conduct a small number of experiments in humans, with mixed results. One problem facing Fleming was that since he did not have a biochemistry background, he could not produce sufficiently pure penicillin to adequately test it (Wainwright, 1990).

Based on the 1929 publication, and through scientific networks, news of the penicillin discovery spread in the United Kingdom first, then globally. While for the next decade there was not much activity, by the 1940s, British government officials actively sought new treatments for wartime infection. This generated interest in penicillin among the British scientific community, including a laboratory at Oxford headed by Howard Florey and Ernest Chain. This group, funded in part by the Rockefeller Foundation, had been working on antibiotics since mid-1930s (Neushul,1993), partly based on successes from sulfa drugs. These two scientists, together with Norman Heatley, are typically credited as being the first to purify penicillin, which made it possible to conduct proper clinical tests. Human and animal tests by these authors showed penicillin to be incredibly efficacious in treating a range of infections.

Following the initial tests, Florey and Chain began thinking about how to produce penicillin at large scale in order to do human trials. While they apparently did discuss the idea with a number of British pharmaceutical firms these firms lacked the ability to mass-produce penicillin (Wainwright, 1990). Moreover, they were not in a good position to develop these capabilities, given wartime time bombings and concerns about possible German invasion.

Florey and Chain shared their techniques with scientists in the US government, including scientists at the US Department of Agriculture's Northern Regional Research Laboratory. The US scientists had long been involved in developing mold fermentation methods (Neushul, 1993), using these to produce a range of chemical compounds.

[4] Domagk could not accept the Prize until after the War, in 1947.

Working with Florey and Chain, the USDA scientists developed a medium for mass production of penicillin, and took out foreign patents for the same. According to Neushul (1993), it was difficult to take out US patents given USDA. Rules on patenting publicly funded research.) Non-acknowledgement of the British collaborators would eventually become the source of controversy, especially in the UK

While this work was ongoing, the US Office of Scientific Research and Development (OSRD), which was in charge of coordinating US research during World War II, worked to convince US firms to become involved in the production effort. While initially pessimistic, reports on the production gains from USDA scientists spurred private interest. The OSRD's Committee on Medical Research (CMR) also helped coordinate clinical testing of penicillin. And the War Production Board helped provide funds to private companies to help transfer to them capabilities and equipment for mass production (Neushul, 1993).

Several large US firms became involved in the wartime penicillin effort, including Pfizer, Squibb, and Merck. OSRD also funded penicillin research projects at a range of universities aimed at overcoming technical hurdles that were encountered when scaling up production. The US government also played an important role in forcing firms to exchange technical information and process technology some of which were patented (Kinella), with one another and with the government (Neushul, 1993). While initially limited to a small number of firms (who made considerable revenue) eventually the government would buy penicillin from any firm with demonstrated capabilities. Achilladelis (1993, p. 287) writes "most pharmaceutical companies jumped on the opportunity of a practically free ride on a lucrative bandwagon and built penicillin plants".

The wartime effort was a great success, increasing production yields from 4 units per milliliter of raw penicillin to to 900 units per ml (of raw penicillin) between 1941 and 1944 (Neushul, 1993). Neushul observes that "this transition, from laboratory, to pilot plant, and finally to mass production took place in an amazingly short period of time" (Neushul, 1993, p. 395). There were no product patents on penicillin, and widespread sharing of process technology compelled by the government. Despite this, wartime subsidies and technical assistance, together with a guaranteed market, made the R&D efforts profitable for the firms that participated (Temin, 1980).

In addition to influencing the course of World War II, the wartime penicillin scale-up changed the pharmaceutical industry. According to Pisano the investments in process technology and capabilities "laid out an architecture for the research process and created a framework in which future improvements could take place" (Pisano, 1997, p. 53). Henderson *et al* (1999, p. 348) argue that the development of penicillin marked the industry's transition from a pre-research period to the second major period in its evolution "characterized by the institution of formalized in-house R&D programs and relatively rapid rates of new drug introduction". Temin (1980, p. 66) argues, similarly, that after the wartime penicillin effort "the drug industry began to transform itself from a typically manufacturing industry to one based on the continual progress of technical knowledge. This transformation involved the development of a new technology, the growth of a new industry structure, a marked intensification of certain older marketing practices".

However, the US government push for wide competition and wide diffusion eventually led to lower prices, and would lead companies involved in penicillin

production to attempt to use their newly developed capabilities to explore other opportunities, including those with more secure patent terms.

Streptomycin

Streptomycin has been described as "one of the two founding discoveries of the antibiotic revolution" (Kingston, 2004, p. 443), along with penicillin. Streptomycin was developed by Selman Waksman, a Rutgers University soil chemist who would also win the Nobel Prize for his work (in 1952). Streptomycin was significant for several reasons, including that neither sulfa drugs nor penicillin had much of an effect on tuberculosis, which was still a major cause of morbidity and mortality in the 1950s.

Waksman's research focus was on actinomycetes, a type of soil bacteria. Even before penicillin, there was a longstanding belief by Waksman and others that soil bacteria may be useful against other microorganisms (Kingston, 2004). Waksman's research on these bacteria was funded by several sources. In addition to several foundations, he was a consultant to Merck, and had an agreement with the firm that provided funding for screening soil samples in exchange for exclusive rights to any patents that resulted. Under the agreement, signed in 1939:

> "The company provided chemical assistance, experimental animals for pharmacological evaluation of antibiotics, and large-scale equipment for producing any promising discoveries. In return, Waksman assigned Merck any patents resulting from research in his laboratory".[5]

The R&D process that led has been described a "mundane" and "a shotgun approach" essentially screening tens of thousands of soil samples for antibiotic activity (Kingston, 2004; Wainwright, 1990). It was apparently so mundane that much of the work was left to his students. In 1943, one such student, Albert Schatz, found bacteria from soil samples and other sources that were effective against tuberculosis, and named the substance streptomycin (There is much controversy about whether Schatz received sufficient credit for the discovery; see Kingston, 2004).

Waksman contacted the Mayo Clinic to conduct trials, using samples produced by Merck. Recognizing the therapeutic potential, Waksman became concerned about giving exclusive rights to a private company, especially since Rutgers had recently become a public university. Much like the Oxford researchers who developed penicillin, US academic researchers at the time were still reluctant to take out patents and exclusive licenses on health related inventions (Mowery and Sampat, 2001a, 2001b). He convinced Merck to instead agree to a non-exclusive license, to keep prices low.[6]

With competition and low prices, there was a sharp drop in deaths after the drug was commercialized in 1950 (Kingston, 2004). Streptomycin became useful against other diseases beyond tuberculosis (typhoid fever, bubonic plague, urinary tract infections, among others) and eventually earned significant revenues for Merck, Rutgers, and Waksman. Together with penicillin, streptomycin diffused globally through a range of UN and US programs distributing US stocks, and new plants were built globally

[5] http://www.acs.org/content/acs/en/education/whatischemistry/landmarks/selmanwaksman.html
[6] www.acs.org/content/acs/en/education/whatischemistry/landmarks/selmanwaksman.html

through UN funded programs (including in China, Czechoslovakia, Italy, Poland, Yugoslavia and elsewhere (FTC, 1958).

The discovery of streptomycin is surrounded by much controversy, much of it focused on patent rights and whether Waksman deserved credit or Schatz also made an important contribution (Kingston, 2004). Streptomycin was also important as a precedent, since it was one of the first cases where a natural drug product was patented, rather than being rejected as a product of nature. The US Patent Office issued "composition of matter" patent to Waksman and Schatz (US 2,449,866, assigned to Rutgers). This was important not only for patentability of this drug but other ensuring patentability of many antibiotics which followed (Kingston, 2001).

The discovery of streptomycin and antibiotics that followed it also led to changes in US patent law. Previously, a "flash of creative genius" was needed to establish patentability. This standard would bar many antibiotic patents, which were developed through well-known techniques. According to Kingston (2001) the New York Patent Bar Association, on behalf of pharmaceutical industry clients, helped draft the 1952 Patent Act, under which "patentability shall not be denied because of the way the invention was made." The Act changed the "creative genius" requirement to "non-obviousness" which may have been more amenable to obtaining patents from routinized large-scale R&D efforts (Dutfield, 2009; Kingston, 2004). Other countries followed the US in enacting obviousness or "inventive step" requirements, including Japan in 1959, Sweden in 1967, France in 1968, and Britain in 1968 (Kingston, 2001).

4- Later Antibiotic Innovations

Synthetic penicillins

One result of the lack of patents on sulfa, the early government involvement in penicillin, and the broad licensure of streptomycin was low prices and rapid diffusion. John McKeen, the President of Pfizer, famously noted "If you want to lose your shirt in a hurry start making penicillin and streptomycin" (quoted in Podolsky, 2015, p. 23). As a result in searching for new antibiotics there was a more explicit focus on limiting competition, including through patents and exclusivity.

In addition to funding the mass production of natural penicillin, the US government during World War II also supported a major research program on the chemical synthesis of penicillin. Previously, organic chemists had achieved some successes in synthesizing sulfa (Bentley, 2003; 2009) suggesting that this might be possible for penicillin as well. During the war, the synthetic program was viewed as riskier than natural production, and encountered scores of unforeseen scientific and technical problems (Sheehan, 1982). While there were some successes, synthetic approaches during the war ultimately yielded very low yields (Swann, 1983). Once the natural production of penicllin achieved great successes, the wartime synthesis program scaled down.

After the war, there was limited enthusiasm for synthesizing penicillin among both government funders and commercial firms (Sheehan, 1982), At least initially, the enormous success of the natural fermentation process also blunted enthusiasm for synthetic penicillins. Many firms were also more enthusiastic about searching for new antibiotics, including those discussed later below, than continued work on penicillin (Jewkes *et al*, 1969).

However, the penicillins developed during the war and shortly thereafter had drawbacks, including difficulty of administration, limited effect on some organisms, and growing resistance (Jewkes *et al*, 1969, p. 352). A small number of labs thus remained active in trying to chemically synthesize penicillin.

After the war, the British firm Beecham Pharmaceuticals had also sought to enter the antibiotic field, where it had little experience. The company engaged Professor Chain from Oxford. (He was by then in Italy, according to some accounts because of his frustrations in difficulties of obtaining medical patents on penicillin when he has at Oxford). In 1957, Beecham scientists and Chain found a way to islolate 6-APA, the penicillin nucleus, from the fermentation broth (Sheehan, 1982). This made it possible to add on side chains to produce "semi-synthetic" penicillins. This provided a platform for the development of many new penicillins. A patent application for isolation of 6-APA was filed in 1957, and the research was also published in *Nature* in 1959.

In the US, John Sheehan, who had worked at Merck but left for MIT, also continued working on synthetic penicillin. He was unable to find government funding for this work, and instead was funded by Bristol Laboratories. Sheehan developed an approach to synthesizing 6-APA that was based on pure chemical synthesis. As Sheehan describes this discovery, "It was clear for the first time in this history of this difficult substance that the penicillin molecule could be modified and manufactured by purely chemical means" (Sheehan, 1982, p. 126). Sheehan filed an application in 1957. Interestingly, the licensure of the Sheehan patents was initially handled not by MIT but by Research Corporation a third party technology transfer agent, the Research Corporation. Research Corporation, founded in 1912, handled academic patents for many institutions in the postwar period. Before the 1970s, US academic institutions were reluctant to become actively involved in patenting and licensing activities, especially for health-related technologies[7]

The British firm Beecham required Sheehan's method for making other penicillins from 6-APA. Moreover, Beecham had limited manufacturing capability, and worked with Bristol to scale up production. Under a licensing agreement Beecham granted Bristol a royalty bearing license to use its patents in the US, Canada, and other non-Commonwealth countries. In turn, Beecham obtained know-how to develop a production plant in the UK

Initially, there was cooperation between Bristol and Beecham. Beecham used several of Sheehan's methods, working with Bristol to produce early semi-synthetic penicillins, including phenethicillin, ampicillin, and amoxycillin. However, this broke down eventually. There was a long legal dispute about whether Sheehan or the Beecham group had priority to 6-APA. This Interference was settled in favor of Sheehan in 1979. Nevertheless, using the technology these firms and others developed many other penicillins, were including ampicillin and amoxicillin, that were significant improvements on the old penicillins.

[7] The Research Corporation acted as a technology transfer agent not only Sheehan's employer, MIT, but also many other US universities. Ultimately Sheehan and MIT decided to use another set of patent lawyers, based on concerns that Research Corporation was not pursuing the patents agressively enough and not considering Bristol (Sheehan's benefactor) seriously enough as a potential licensee. These problems resemble more general principal-agent issues in third party technology transfer (Mowery and Sampat, 2001).

Other antibiotics

Following streptomycin, other firms also began searching soil samples for antimicrobial activity. Two of the early successes were chlortetracycline (Auereomycin), oxtetracylcine (Terramycin) and tetracycline (Tetracyn, Achromycin) (FTC, 1958). These drugs, the first generation tetracyclines, are notable since they are broad spectrum antibiotics: active against both gram negative and gram positive bacteria. They were developed by Lederle Laboratories, Pfizer, and Lederle/Bristol Laboratories respectively (Landau *et al*, 1999). Another early broad spectrum antibiotic was chloramphenical (chloromyctin). Three of the broad spectrum antibiotics (chloratetracycline, oxtetracycline, and chloromphenicol) were patented and produced exclusively by the patentee. Tetracycline was the subject of a patent interference suit and considerable litigation, discussed below.

Another important early class of drugs was cephalosporins. These were based on a discovery by Giuseppe Brotzu (in Sardinia), who, inspired by the success of penicillin, searched for molds in a local sewer (Landau *et al,* 1999). He found Cephalosporium acremonium. This drug was important since it had broader spectrum than penicillin, and other benefits. (Landau *et al,* 1999).[8] Finding it difficult to get people interested in Italy, on the suggestion of a colleague Brotzu sent a sample to Florey and Heatley at Oxford. Researchers at Oxford and found a range of cephalosporins, and developed techniques to create semi-synthetic cephalosporins.

When Florey and Chain did their penicillin work there decades earlier, there was a feeling that academic medical research ought not be patented. However, aiming to stimulate the postwar economy and resentment about losing penicillin to the US (Dutfield, 2009, p. 144) created a more pro-patent position in the UK, and at Oxford. The National Research Development Corporation (NRDC) was established in the UK on 1949, aiming to foster the development of inventions in the national interest through managing patents. NRDC filed for a number of patents, which were initially licensed to Lilly and Glaxo but later also a number of companies globally (Abraham).

Still other classes of antibacterials were developed in the years that followed, including anti-tubercular drugs, nitroimidazoles, chloramphenicols, quinolones, monobactams, augmentin, and primaxin (Landau *et al,* 1999) there was innovation on many dimensions, including new classes of drugs, development of drugs effective against different types of bacteria, drugs with better side effect profiles, and improvements in route/ease of administration (Achilladelis, 1993).

The Evolution of the Pharmaceutical Industry

For most of the new antibiotics, patenting the drugs' active ingredient and producing exclusively became an important part of commercial strategy (Temin, 1980; Achilladelis, 1993). Previously, product and process patents were licensed to other producers by their owners. With the new wave of antibiotics, firms began to use their active ingredient patents to enforce monopoly positions, leading to the first wave of

[8] "Brotzu was more isolated in Sardinia than Fleming was 17 years earlier in St. Mary's Hospital and accordingly, the development of cephalosporins took longer than that of penicillin. He had no means , or knowledge to identify the active metabolites so that – like in penicillin – advanced was made when the fungus was sent via the UK National Research Development Corporation to Oxford University were some of the workers of the original penicillin team still worked."

concerns about high drug prices. FTC (1958) provided data suggesting that the early penicillins and streptomycin had broad production, but antibiotics introduced later typically had one or a few producers. (The FTC report also shows similar growth in concentration of antibiotic patent ownership between the 1940s and 1950s.)

In addition to patenting, much like the Germans had done with sulfa drugs decades earlier, firms began using trademarks aggressively to try to strengthen and lengthen monopoly periods. This was particularly important since significant within-class competition that exerted price pressure on early antibiotics (Temin, 1980). By 1954 there were over 100 antibiotics marketed under over 500 trade names which evidently created much confusion for physicians (Welch 1954).

Related to this, firms began investing in marketing to doctors. Most major companies invested heavily in expanding their sales forces. As a result "Marketing and sales became at least as important in R&D for pharmaceutical companies which spent an average of 30-35 percent of their sales for the former and 10-16 percent for the latter" (Achilladelis, 1993, p. 288).

This, in turn, according to Temin (1980), was important for market structure. Companies transformed themselves into vertically integrated firms with research, manufacturing, and sales arms, focused on discovering, making, and selling drugs. There were scale economies in detailing, which contributed to concentration. Patents and trademarks, together with aggressive marketing, became essential aspects of the business model.[9] Another strategy was pooling, or what some have called price fixing and cartelization. When the three broad-spectrum antibiotics were developed independently three firms, and turn out to have chemical similarities, the firms not only became active in marketing and product differentiation, but also concerned about overlapping patient claims. Rather than rely on the patent office to establish priority, they reached agreements to divide up the market and (it was alleged) exclude competitors.

The rise of aggressive marketing and concerns about anti-competitive activity led to calls for regulation. The conventional view is that drug regulation grew in response to reports of birth defects from thalidomide, a drug often taken by pregnant women to ameliorate morning sickness. Recent scholarship suggests that the role of thalidomide was more subtle. The growth of drug regulation originated with concerns about prices, concentration, and patents, much if it surrounding antibiotics. In the US, beginning in the 1950s the Kefauver hearings scrutinized pharmaceuticals and other industries, motivated by concerns about concentration. A particular concern in pharmaceuticals was over prescribing of fixed dose combinations–combinations or existing antibiotics (e.g penicillin and streptomycin) which were being widely marketed with little evidence of effectiveness, and were contributing to bacterial resistance (Podolsky 2015).

[9] The most detailed study of market structure in antibiotics is the study of penicillins by Klepper and Simons, who use detailed data on market structure of penicillins to test different models of how industry structure evolves. For this technology, as for several others studies by the authors, there was rapid entry after the initial innovation (during and after World War II), slower entry thereafter, then consolidation and exit, or "shakeout." Consistent with this story, much of the production of penicillin into the 1970s was by firms who were involved in wartime production and initial postwar development. Klepper and Simon interpret the finding that the same firms remained dominant is interpreted as consistent with theories emphasizing increasing returns to R&D (those with large output had lower per unit R&D costs). Klepper and Simon more qualitative analysis suggests that the initial expansion may have reflected a lifting of wartime restrictions on production. The development of synthetic penicillins facilitated a round of new entry, by providing an innovation platform, though the strongest firms were incumbents.

Among other fixes, the legislation aimed to create an efficacy standard at the FDA to ensure that new drugs worked (Carpenter, 2014), and to eliminate patents for "me too" and FDC drugs. The bill also included provisions for compulsory licensing, essentially allowing entry at three years for reasonable royalties. For various reasons—including strong opposition by the drug industry to the patent provisions — the bill had stalled by the early 1960s (Carpenter 2104). Then the thalidomide tragedy came along, and created political momentum to revive ideas from the Kefhaver bill, those focused on efficacy. (The patent provisions were absent from the revised bill.) This change helped create the modern FDA, by institutionalizing the need for randomized clinical trials before drug approval (Carpenter, 2014).

European regulations remained weaker. In Germany, even in the wake of thalidomide there was strong opposition to drug regulation (Carpenter, 2014) and a belief the pharmaceutical industry could self-regulate. In other countries such as Britain and France there were calls for change, but most countries' regulatory structures remained weaker than the US. Across Europe, there was considerable variation in national drug regulations until at least the 1990s (Vogel, 1988). Reflecting tougher US regulations, there emerged an academic literature about the "drug lag" caused by development of the 1962 FDA — the share of drugs that were being delayed due to US regulation but were introduced elsewhere (Temin, 1980).

The rise of regulation has its roots in concerns about negative effects of patent monopolies in antibiotics (overprescribing, high prices). It is striking that the resulting rise of regulations are themselves a commonly cited reasons why patent protection is more important in pharmaceuticals than other fields. On onee hand, trials increase costs of R&D significantly, making the need for long patent terms (to recoup expenses) greater. On the other, the need for trials make inventing around a patent harder: One can tweak a molecule, but it is costly to introduce this changed molecule to market, requiring expensive new trials. Here again, technology and the institutions governing the industry co-evolved.

5- The Roles of Patents in Antibiotic Innovation

What roles did patents have in the breakthrough discoveries? For the sulfa drugs, is clear that patents were very much a focus of the German effort to discover and develop sulfa drugs. Based on Hager's (2006) account, Hörlein, the head of drug research at Bayer, was apparently very focused on patents.

> "He knew that most researchers had given up on Ehrlich's magic bullets, convinced after years of fruitless searching that synthesis medicines were little more than a dream … He figured the search would take years. And he expected hundreds of failures along the way. But he had faith. One success against bacteria, just one, could open an entire field, lead them to a host of patentable drugs." (Hager, 2006, p. 95)

One of the main theoretical benefits of patents is that they promote disclosure. In this case, there was so much concern about this disclosure effect that were delays in filing patent applications (and publicizing the invention) until other variants of sulfa were found:

> "Publicizing Streptozon threatened to draw the attention of the rest of the world's drug firms, possible poachers on Bayer's preserve. There was no way to protect the area forever, because their work already showed that any number of azo-dye

derivatives could be active as medicines.; Bayer could not patent them all. But delaying publicly about Streptozon gave Bayer time to find and patent the best of them." (Hager, 2006, p. 150)

Moreover, given concerns about reverse engineering, Bayer apparently aimed to write its patents to prevent complete disclosure.[10] Despite these attempts to obfuscate, the publication of the main sulfa patent led to some disclosure. After it issued, according to Hager (2006) "[A]nyone who wanted to know how to make Streptozon, at least in vague terms, could now look it up" (Hager, 2006, 150). And this experimentation apparently allowed the French researchers to identify sulfanilamide, and old molecule, as the key ingredient.

The discovery was certainly incentivized by patents. However, in most countries only process patents were available at the time of discovery. And, the unexpected discovery that the old molecule with no patents was the key to production helped spur competition, and perhaps even subsequent innovation. So in the sulfa story we see patents inducing innovation but not actually restricting access, but only because the patents were found to be ineffective after the discovery was made.

In contrast to sulfa, the penicillin story is typically viewed as one where patents did not play much of a role at all (Bentley, 2009). While some have suggested that Fleming's non-patenting of penicillin was one reason why it took so long to get commercialized, Robert Cook-Deegan has dismissed this claim, noting "[Penicillin] was indeed not patented, but it was also not fully characterized and it is not clear it was described with sufficient precision to warrant a patent. Moreover, for the limited utility that Fleming wrote about in his papers, there was little reason to patent penicillin" (see Kinsella, Stephan: "Patent and Penicillin",http://mises.org/blog/patent-and-penicillin).

At the Oxford group, evidently Chain had wished to patent penicillin but this was the source of some tension between he and Florey. Florey, like many medical researchers at the time, believed it unethical to patent the results of publicly funded research (Mowery and Sampat, 2001a, 2001b). Moreover, patenting would have been difficult given penicillin mold was a natural product. (Bentley, 2003). And in any case, product patents in pharmaceuticals were not available in the UK at that time, and the process had been disclosed in a publication before Chain became interested in patenting the discovery (Bentley, 2003).

The US firms involved in penicillin production, and scientists at Department of Agriculture, had taken out patents on the production process. This caused some discord among the British researchers alleging the the US researchers had privatized a public UK discovery (and, later, forced UK firms to pay royalties on the technology). Whether or not this is true is the subject of considerable debate, but the belief that the UK lost out on penicillin apparently led UK researchers to be more aggressive in patenting other medical discoveries down the road (Bentley, 2003, Wainwright, 1990). It may have also led Chain to leave the UK for Italy, after the war.

The fact that there were few product patents on penicillin meant it was widely available at low cost. The eventual difficulty in profiting from penicillin also led firms to be more focused on exclusivity in subsequent R&D efforts.

[10] "[German] chemical patents were often written in ways that described the process while at the same time lessened the chance of duplicating it. The wordsmiths in Bayer's patent office were masters of twisting, subtle language that rivaled that of the most obscure modern novelists" (Hager, 2006, p. 140).

In the case of streptomycin, on one hand the research agreement between Merck and Waksman was explicitly about discovering antibiotics that would be patented. Even after the drug was discovered, Merck's interest in the patent was certainly crucial to its decision to to help supply the drug for and participate in clinical trials. As discussed above, the granting of a composition of matter patent was an important precedent for the pharmaceutical industry, as was the emergence of the non-obviousness requirement. On the other, given uncertainty about patent laws for natural substances at the time, Merck could not have been sure about its ability to obtain a strong patent, but nonetheless funded the research. And once the patent was obtained, it was licensed broadly. Here is is unclear exactly how important the prospect of an exclusive patent was to inducing the initial research.

Temin (1980) flags a different dimension: "Waksman developed not just a new drug but a new research tool –The technology of searching soil samples and other natural sources for antibiotics." The research tool was kept in public domain, and Temin appears to argue that this was important for the discovery effort: "Patents, therefore, were important for the development of the drug industry both for what could be patented (after streptomycin) and for what could not." This is consistent with the idea advanced in Merges and Nelson (1990) and others that keeping broad research tools in the public domain is important for promoting follow-on innovation.

In the breakthrough innovations, the importance of patents for incentivizing innovation is mixed. By contrast, they clearly had an important role in the development of the later antibiotics. The search for these antibiotics was explicitly about developing new, exclusive molecules, in an era where price competition on both first generation penicillin and streptomycin made the industry unprofitable.

For example, Taylor and Silberton (1973) directly asked a spokesperson for the Beecham group on the role of patents in the discovery of semi-synthetic penicillins. Specifically, the group was asked what would have instead happened under a regime of compulsory licensing, i.e. where licenses to the invention could not have been refused.[11]

According to their summary:

> "The original decision to expand drug research would probably not have been taken, and basic work such as that which led to the discovery and development of the new penicillins would not have been launched. Beecham would have continued to rely essentially on its traditional product lines … Had effective patent protection been generally available, but not on penicillins, the research would have proceeded in other pharmaceutical directions. Had active requests for compulsory licenses materialized after the launching of the penicillin program, the main ultimate effect would probably have been to cut the program hard back, as royalty receipts would have been much lower in these circumstances and they have been very much the mainstay of new research. Moreover, had effective patent protection been lacking in the USA, it would have been extremely difficult to persuade Bristol Myer to divulge its manufacturing know-how" (Taylor and Silberton, 1973, p. 259).

[11] This was part of Taylor and Silberton's broader study of the patent system; they considered this a better counterfactual than assuming no patent protection at all.

Sheehan's own account is consistent, suggesting that the prospect of patents was much more important to drug companies for synthetic pencillins after the war than for natural penicillins during the war (Sheehan, 1982, p. 77).

As was true for Chain and Florey at Oxford, Sheehan faced difficulties in patenting penicillin at MIT, reflecting academic qualms about patenting public health related inventions (Sheehan, 1982). However, it ultimately did so, on the theory that it would be a better steward of the patent than if others instead obtained the patent. Part of Sheehan's own motivation for obtaining a patent was to be able to more freely collaborate with Bristol.

To summarize, at least according to their inventors, patents appear to have been important for incentivizing innovation for semi-synthetics. The prospect of patents also motivated other new antibiotics, including the broad spectrum antibiotics and cephalosporins. At the same time, interferences and litigation also became commonplace for the new classes of antibiotics, perhaps evidence of the patent system inducing "racing" behavior. Many of these interferences resulted in settlements with cross-licensing, which in turn raised anti-competitive concerns. More generally, the focus on patenting (and complementary strategies, including trademarks and marketing) and exclusive production generated the first wave of concern about high prices.

What about patents and global diffusion, or access to medicines? All of these breakthrough inventions diffused rapidly within industrialized countries, and at low cost. Patents did not get in the way, but for different reasons across the cases. For sulfa the base compound was discovered to be unpatentable. Jayachandaran *et al* (2010) and others suggest that this lack of patentability helped spur broad diffusion. The same is true of penicillin. For streptomycin Merck licensed broadly in the face of public pressure to do so.

The availability of product patents was also not widespread, even among developed countries, until the late 1960s. And, certainly, most developing countries did not y*et al*low for pharmaceutical product patents until after the 1995 Trade Related Intellectual Property Rights (TRIPS) agreement (Deere, 2008). Several scholars have noted that despite this it took considerable time for the breakthrough antibiotics to diffuse to developing countries (Cutler *et al*, 2006), and many of the infectious diseases they treat remain problems even today. Some have interpreted this as evidence suggesting that patents may not be a major part of the access problem.[12] There is however no direct evidence on the effects of patents or non-patenting on diffusion or access in developing countries.[13]

6- Conclusion

There is no doubt that sulfa, penicillin, and streptomycin were among the major breakthrough innovations of the twentieth century. In this concluding section, I discuss the key features of the innovation process, and aspects of the innovation system that helped support these innovations.

[12] Cutler *et al* (2006) observe "the fact that many countries cannot deliver the cheap, effective, and widely available drugs that currently exist has been a persistent argument by those who doubt that the patents on antiretroviral drugs can be blamed for the lack of success in dealing with HIV/AIDS in Africa."
[13] Chaudhuri *et al* (2003), in a study of another antibiotic class, quinolones, estimate that pharmaceutical product patents in India would have resulted in large welfare losses for Indian consumers, $144 million to $450 million annually

War was crucial to the development of two of the three breakthroughs, sulfa and penicillin. In the sulfa case, disruptions caused by the First World War motivated the German R&D efforts. In the penicillin case, the urgent need for effective treatment during the Second World War fueled the massive US wartime development and production program. Rosenberg (1969) has suggested that wartime disruptions can be an important inducement to technical change. More recently, Ruttan (2001, 2006) suggests military procurement and defense R&D are important in the development of "general purpose technologies." What is interesting in both the sulfa and penicillin cases is that while wartime disruption and urgency undoubtedly contributed to demand for innovation, both of these innovations built on pre-existing science. War may have spurred more rapid exploitation of this science. This is the position taken by Vannevar Bush in *Science, The Endless Frontier,* sometimes considered the blueprint of US science and technology policy. There (after discussing penicillin other wartime medical breakthroughs) Bush asserts "The striking advances in medicine during the war have been possible only because we had a large backlog of scientific data accumulated through basic research in many scientific fields in the years before the war." The role of wartime exigencies in spurring new science and technology, versus the exploitation and adaptation of existing technologies, is an interesting question for future research.

One thing that is clear is that there were strong links between science and technology, between academics and industry, in all three of the breakthrough inventions and the follow-on antibiotics. The channels through which academics contributed to industrial innovation varied over the cases: from "simply" doing the fundamental research (Fleming), to developing embryonic ideas that were developed by industry (Chain and Florey), to working with industry funded to develop a potential product (many of the other cases). The channels through which academic research was transferred to industry were also diverse, including publication, consulting, and labor mobility. In some of the the latter cases licensing of patents to firms occurred, but in a very different way than is common today. First, in almost all cases, academics were somewhat nervous about patenting public health related technologies, and academic institutions not eager to get involved in the nitty gritty of these activities (Mowery and Sampat, 2001a, 2001b). This in turn affected both the academic institutions aggressiveness in licensing patents, and (in the streptomycin case) the extent of competition the licensee allowed. In the US, academic institutions reluctance to be involved in patenting and licensing medical inventions faded over the decades that followed. And through a range of developments, culminating with the 1980 Bayh-Dole Act, federal policy supported patenting and exclusively licensing the results of public medical research (Mowery and Sampat, 2001a, 2001b). Whether and how this focus on patenting and licensing has influenced the other types of university-industry interaction and channels of technology transfer that were important for the breakthrough innovations remains unclear (Mowery *et al,* 2004).

Another theme that cuts across several of the cases (penicillin, streptomycin, synthetic penicillin) is the importance of process innovation in securing gains from product innovation, the difficulties in sharing the often tacit aspect of production processes, and the resulting need for need for collaboration and partnerships to commercialize new technologies. The sulfa case suggests that process innovation may also have been an important source of intellectual property protection in the era before drug product patent were widespread.

What about the roles of patents in the development of these breakthrough inventions, more generally? The pharmaceutical sector is typically characterized as one industry where patents are both essential for appropriability and innovation incentives, and

where they are effective at excluding competitors (Levin *et al,* 1987; Mansfield, 1985; Taylor and Silberton, 1973). For the three breakthrough innovations—sulfa drugs, penicillin, and streptomycin–patents had more subtle roles than this characterization would suggest. For two of the three (sulfa and streptomycin) patents may have been important inducements to innovation. But for none of these inventions did patents really restrict access. And the technological platforms and basic techniques associated with the three breakthrough cases were kept relatively open, in the sense that there were few patents or exclusive licenses, which some observers (e.g. Temin, 1980) suggest facilitated follow-on innovation.

Though the antibiotic revolution in many ways created the pharmaceutical industry, the industry changed dramatically in the years that followed, in large part as a result of this revolution. As the discussion of broad-spectrum antibiotics suggested, the initial breakthrough innovations generated profits and created capabilities which would later be deployed in the search for other antibiotics, and other drugs. Across all drug classes, this later search was explicitly focused on getting patentable inventions which were produced exclusively.[14] This was supported by large vertically integrated firms active in research. Patent litigation, and races to obtain patents, became more common. Once firms obtained patents, there was heavy marketing of drugs. This growth of marketing and concerns about inappropriate utilization and high prices, in turn, led to new drug regulation. These are thought to have raised the costs of drug development, and perhaps also the importance of patent protection (Grabowski and Vernon 2010). One lesson from the breakthrough inventions is that science, technology, law, and strategies co-evolve. This makes it very difficult to tease out the causal role that patents and other intellectual property rights have on innovation. It is difficult to say how the development of the breakthough antibiotics would have played out with weaker (or stronger) patents. It is more clear that the antibiotic revolution helped create the modern patent-intensive pharmaceutical industry, by creating capabilities and profits that generated subsequent innovation, and by shaping patent laws, patent standards, and firm patent strategies.

[14] Temin (1980) notes this model spread throughout the drug industry: "A similar stepwise development of drug patents took place (with less publicity) in steroids about five years later. The first steroids, cortisone and hydrocortisone, were not patented. The first synthetic steroids, prednisone and prednisolone, were introduced in 1955. The were patented but the patents were licensed widely. Only with the second generation of synthetic steroids and the birth control pills of the 1950s was the pattern of exclusive production widespread … Exclusive production replaced unrestricted patent licensing throughout the drug industry."

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