

THE FORGOTTEN ORIGINS OF ANTIMICROBIAL RESISTANCE

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Abstract

The evolution and spread of resistance to antimicrobial drugs is currently viewed as a growing public concern, being ranked alongside other major threats such as climate change and terrorism. Interestingly, antimicrobial resistance is most often framed as a recent phenomenon, which results from the use and abuse of antibiotics in the clinic and husbandry. According to this view, the antimicrobial drugs used before the 1940s did not drive the emergence of resistance outside the laboratory and, therefore, antimicrobial resistance was not perceived as a clinical problem at the time. This dissertation challenges this view. By surveying major biomedical articles and textbooks on the treatment of syphilis with Salvarsan—one of the earliest antimicrobial drugs available in medicine—I show here that clinical antimicrobial resistance is older than we think, and that it motivated a reciprocal exchange of knowledge between the laboratory and the clinic, which have been claimed distant in the first decades of the 20th century. Importantly, the key primary sources used and analysed in this dissertation have hardly been cited by biomedical researchers and historians in their works on the history of antimicrobial resistance, despite being published in top-tier journals on syphilology and its treatment. This aspect begs the question: Why was the earlier history of drug resistance forgotten in these accounts? I argue that the historical amnesia about arsenic-resistant syphilis that I explore in this dissertation is consistent with what is known about the historical amnesia of biomedical knowledge more generally.

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- Introduction -

This dissertation is about the history of drug resistance. It uncovers the early history of resistance to antimicrobial drugs in the clinic, which has been unexpectedly overlooked by historians of medicine. Why explore the history of drug resistance? In my case, the answer to this question is twofold. First, I study the biology of antibiotic resistance, and I thought that a historical approach to the problem could provide me with a wider perspective to one of my science research topics. In particular, I thought that a historical approach could help me to contextualize the problem better, and to understand how our perceptions about it have been changing over time. Indeed, one should not forget that antibiotic resistance is both a natural phenomenon and a social construction, and by the latter I mean that its definition is subjective and historically contingent. Arguably, and as I will elaborate in more detail in the next chapters, the scientific consensus about this problem has changed over time, but the societal one has changed as well. An historical perspective is key for appreciating such temporal changes, as it is also key to understanding the unescapable continuities.

But in addition to this reason for exploring the history of drug resistance in this dissertation, there was another one. When I started this MA in the History of Medicine, and as a novice in the field of history, I serendipitously came across with an interview with the historian of science Simon Shaffer in which he claims that “the problems historians ask are problems always suggested by our contemporary situation. The only danger is to forget that fact and to pretend that the past effortlessly produces its own questions”. Around the same time, and again serendipitously, I read

the book *The Scientific Life*, in which the author—the historian of science Steven Shapin—makes a similar claim in the book’s preface, saying that “we *inevitably* write about the past as an expression of present concerns, and we have no choice in this matter”.¹ These words have resonated with me ever since. They made me think about present concerns in medicine, and about what was known of their history. And while 21st-century medicine is faced with very many problems, few (if any) have been framed with the same level of apocalyptic rhetoric as the problem of drug resistance.

In particular, antimicrobial resistance (i.e., resistance to antimicrobial drugs²), has been framed as a growing public concern, and it is now ranked alongside major threats such as terrorism and climate change. Dame Sally Davies, the previous Chief Medical Officer of Great Britain, put it clearly when in 2013 she made her famous claim:

Antimicrobial resistance is a ticking time bomb not only for the UK but also for the rest of the world. We need to work with everyone to ensure the apocalyptic scenario of widespread of antimicrobial resistance does not become a reality. This is a threat arguably as important as climate change for the world.³

More specifically, antimicrobial resistance has been described as a major threat to global health, food security, and socio-economic development, being predicted to cause 10 million human deaths annually, and a cumulative cost of \$100 trillion by 2050.⁴ It is thus not surprising that

¹ Shapin S (2008) *The Scientific Life: A moral history of a late modern vocation*. The University Chicago Press, London. Preface page xiii, italic in the original. I am aware that not all historians agree with this claim, and indeed Shapin briefly discusses this issue. However, one should note that the arguments presented in this dissertation do not rest on this idea. It simply guided me towards the specific theme of the dissertation.

² I will discuss in detail the meaning of the concept “antimicrobial resistance” and how it changed over time, in Chapter 3. For now, it can be understood as a form of drug refractoriness.

³ Davies SC (2013) *Annual report of the chief medical officer (vol 2)*. Department of Health, London.

⁴ Adeyi OO, et al (2007) *Drug resistance infections: a threat to our economic future (vol 2): final report (English)*. World Bank Group, Washington DC.

antimicrobial resistance has become a major research topic in biomedical sciences and a key strategic priority for multiple funding bodies worldwide.

Not coincidentally, antimicrobial resistance has become a research topic for historians, namely those interested in the history of medicine. More often than not the subject is imbedded in broader narratives about the discovery and use of antimicrobial drugs such as antibiotics, with focus on their social and cultural impact. Excellent examples of such narratives include Robert Bud's *Penicillin: Triumph and Tragedy*, Scott Podolsky's *The Antibiotic Era*, and John Lesch's *The First Miracle Drugs*.⁵ But there are also some works dedicated to the history of antimicrobial resistance, such as Podolsky's "The evolving response to antibiotic resistance", William Summers' "Antimicrobial Drug Resistance" and Christoph Gradmann's "Magic bullets and moving targets: antibiotic resistance and experimental chemotherapy, 1900-1940".⁶ The topic has also been covered by many other authors who, despite not being professional historians, also tell interesting and relevant stories about the history of antimicrobial resistance. Among these works, Stuart Levy's *The Antibiotic Paradox* and Carol Morberg's "René Dubos: A Harbinger of Microbial Resistance to Antibiotics" are arguably some of the most famous examples.⁷ Obviously, the history of antimicrobial resistance is often briefly covered by

⁵ Budd R (2007) *Penicillin. Triumph and Tragedy*. Oxford University Press, Oxford; Lesch JE (2007) *The First Miracle Drugs. How the Sulfa Drugs Transformed Medicine*. Oxford University Press, Oxford; Podolsky SH (2015) *The Antibiotic Era. Reform, Resistance, and The Pursuit of a Rational Therapeutics*. Johns Hopkins University Press, Baltimore.

⁶ Gradmann C (2011) Magic bullets and moving targets: antibiotic resistance and experimental chemotherapy, 1900-1940. *Dynamis* 31:305-21; Podolsky SH (2018) The evolving response to antibiotic resistance (1945-2018). *Palgrave Commun* 4:124; Summers WC (2008) "Microbial Drug Resistance: A Historical Perspective" in *Bacterial Resistance to Antimicrobials* (eds Wax RG et al.), 1-9 CRC Press.

⁷ Levy SB (2002) *The Antibiotic Paradox. How the Misuse of Antibiotics Destroys Their Curative Powers*. 2nd edition. Perseus Publishing, Cambridge MA; Moberg CL (1999) René Dubos, A Harbinger of Microbial Resistance to Antibiotics. *Persp Biol Med* 42(4):559-80. Moberg's work is not focused on the history of antimicrobial resistance itself, but on René Dubos and his premonitory views about the problem.

microbiologists, evolutionary biologists and biomedical scientists in their science articles and reviews. But here the clinico-biological features of the issue, not the history, have the spotlight.

How can one contribute to a field that has been getting high (and increasing) attention? Put differently, what hasn't been explored about the history of drug resistance that would allow me as a historian and a microbiologist to make a novel contribution to both fields? One of the aspects I found more peculiar about the historiography of antimicrobial resistance is its temporal frame. The vast majority of works on the topic focus on the mid-20th century onwards. Indeed, antimicrobial resistance is understood as a recent phenomenon, a result of the misuse and overuse of antibiotics and other antimicrobial drugs in the clinic and agriculture, whose origin can be traced back to the 1940s.⁸ According to this canonical view, therefore, chemotherapy before this period did not struggle with drug resistance, or at very least that history has not been perceived as having enough merit to be told. With very few exceptions such as Gradmann's work, mentioned above, or Da Silva & Benchimol's "Malaria and Quinine Resistance",⁹ which I will properly introduce and discuss in detail in Chapter 3, the historiography of antimicrobial resistance by and large overlooks the first decades of the 20th century. It is certainly true that the quantity and diversity of antimicrobial drugs available before the 1940s was very limited when compared to what was offered after World War Two, particularly after the introduction of

⁸ Just to clarify, I am not considering here the view of antimicrobial resistance as a natural phenomenon, which can result from microbial interactions in the environment. Microbiologists who study microbial ecology and evolution do appreciate that antimicrobial resistance is ancient, but this biology is hardly appreciated by medical historians, medical doctors, and the general public at large. Either way, the antimicrobial resistance I consider in this dissertation is the one that results from human action, namely the one that emerged with chemotherapy.

⁹ Da Silva AFC, Benchimol JL (2014) Malaria and Quinine Resistance: A Medical and Scientific Issue between Brazil and Germany (1907–19). *Med Hist* 58:1-26.

antibiotics in the clinic. But this aspect alone does not justify our lack of understanding about antimicrobial resistance in the first decades of the 20th century.

This neglect drove my attention to the topic. Moreover, there seemed to be a consensus in the field (even if most often implicit) that is hard to understand if I put on my microbiologist's hat. As some authors claimed, “[R]esistance as a concern for clinical medicine only became relevant during the Second World War”.¹⁰ Gradmann, for example, has argued that the history of drug resistance in the first decades of the 20th century is fundamentally different from the one that emerged after 1940. According to this view, early drug resistance was recognized, and was indeed studied in the laboratory. However, it was absent from the clinic.¹¹ How can it be that drug resistance was not a clinical problem before 1940? Was the phenomenon absent from the clinic or it was present, but it was not reported as such? Alternatively, was the evidence documented but then ignored? I, therefore, decided to look for cases of drug resistance in the clinic before 1940 in hopes of supporting, or challenging, Gradmann's claim.

By surveying some of the most respected biomedical journals and textbooks of that time, I found a plethora of sources discussing antimicrobial resistance in the clinic before 1940, including both laboratory and clinical reports led by physicians and biomedical researchers, and reviews covering hundreds of works on the topic. In particular, arsenic-resistant syphilis was extensively debated in the early decades of the century. Clearly, antimicrobial resistance was not “absent from clinical medicine” as recently concluded. Intriguingly, as far as I can tell, none of these

¹⁰ Santesmases MJ, Gradmann C (2011) Circulation of antibiotics: an introduction. *Dynamis* 31(2):293-303.

¹¹ The key work where Gradmann explores the history of antimicrobial resistance in the first decades of the 20th century is “Magic bullets and moving targets” mentioned in footnote 5. I will revise the argument of the author in a dedicated section of Chapter 3.

works has been explored by historians of medicine.¹² This observation then begged the answer for the following question: Why did we forget this early history of antimicrobial resistance? Ultimately, this is what this dissertation offers; it uncovers and analyses a multiplicity of primary sources on the early history of antimicrobial resistance and offers a rationalization, even if provisional, for why such history has been forgotten and is now neglected by medical historians and other researchers. The rationalization is arguably tentative only, namely because human societies do not often leave explicit records for why they do not consider something as relevant to remember, and this seems to be the case for the early history of antimicrobial resistance. The rationalization I provide is, however, consistent with what we know about how biomedical knowledge more generally is forgotten, and I will discuss these aspects in detail in Chapter 4.

As I was surveying the historiography of chemotherapy, however, I realized that the vast majority of works are devoted to what is typically called the “antibiotic era”, with narratives in which this period is understood as starting in the 1940s with the introduction of Penicillin in the clinic. The very first decades of chemotherapy, which date back to the late-19th century, are rarely mentioned in such narratives. Despite this neglect, later decades are typically pictured as revolutionary. The 20th century is indeed most often described as a period of therapeutic revolutions, and this perspective has been challenged by historians of medicine.¹³ But still, the earlier decades of chemotherapy are not used in their arguments.

¹² These works have also not been explored by modern biomedical researchers, namely those who study drug resistance. But I find it more intriguing that historians who specifically explore the history of drug resistance have neglected these primary sources, than biomedical researchers who only briefly cover the earlier history of their subject in their published work.

¹³ The classical work on the topic is Charles Rosenberg’s “The Therapeutic Revolution”, Rosenberg CE (1977) *The Therapeutic Revolution: Medicine, Meaning, and Social Change in Nineteenth-Century America*. *Perspect Biol Med* 20(4):485-506. I will discuss this and more recent works on the topic in the next Chapters.

How can something be considered revolutionary, or not revolutionary, if its early history has not been contemplated? More precisely, what are the key differences of the drugs available after the 1940s, and our perceptions about them, when compared with those available before this period? What makes them revolutionary, or not, when compared to earlier drugs? As I was pondering about these questions, I realized that our current periodization of the so-called “antibiotic era”, according to which it started in the 1940s, and the idea that it represents a dramatic change in medicine, should be revised in a dissertation on the early history of antimicrobial resistance. The fact that antimicrobial resistance was present in the clinic in the first decades of the last century, as I unveil here, and that this problem is now often understood as a defining feature of the antibiotic era, already suggests that this period arguably needs to be broadened. But one does not need to invoke the early emergence of drug resistance to make such a claim. Instead, this feature can be understood as a natural consequence of the similarities between the two periods, before and after the 1940s, when it comes to the uses and abuses of chemotherapy. I will explore this idea below in Chapter 2, where I will also revisit the very concept of “antibiotic” and its changing meaning. These celebrated drugs became part and parcel of our lives in the last decades and are now so commonplace in medicine that we hardly ponder about what distinguishes these drugs from others, and if our conceptions have changed over time. They did change, and this aspect should be considered when we discuss the virtues and vices of the antibiotic era.

As is expected in scholarship, historical or scientific, my conclusions here rest on the evidence I gathered and how I mobilized this evidence in my claims. In spite of finding what I consider sound evidence for my leading arguments, I must acknowledge the limitations of my approach. I

focused in this dissertation on some of the most respected biomedical journals and textbooks on pharmacology, which introduce and discuss syphilology and its treatment in the first decades of the 20th century. These primary sources do show active discussions about early drug resistance in the clinic. However, I mainly used English literature with a focus on the British and American context, and it can certainly be argued that this literature is not representative of what can be found in other countries and languages. Importantly, other historians have explored other contexts to understand the early history of drug resistance. For example, Gradmann focused on German literature and, therefore, it can be argued that we arrived at contradictory conclusions simply because we studied different social contexts. While I acknowledge my methodologic limitation, I highlight that I explored the works of some of the world experts in the field, such as Dr Beerman and Dr Sequeira (American and British doctors, respectively), who were very knowledgeable about what was happening in other countries at the time, and indeed considered the German and the French case as particularly problematic regarding arsenic-resistant syphilis. Dr Beerman, for example, published large reviews on the problem where he compiled hundreds of sources that were produced by a variety of actors, including biomedical scientists and physicians, from Europe and America. By focusing on some of the experts in the field I tried to moderate the limitations mentioned above, but I appreciate that there is room for improvement.

Arguably, this work can be viewed as a form of intellectual history, broadly defined as the study of ideas, intellectuals, and intellectual patterns over time. Indeed, I tracked the changing meaning of ideas such as “drug resistance” and “antibiotic” over time, as well as some of the intellectuals who contributed to the discussion about these concepts. However, I left silent other actors such as the patients who actually took the drugs and eventually experienced drug refractoriness during

their treatment. What did patients think about the phenomenon of “drug resistance” and how has this perception changed over time? Importantly, how did it affect their daily lives? I appreciate that their voices are not considered in this dissertation, and indeed they are most often left silent in the historiography of antimicrobial resistance. From my side, I can say that my decision to leave these voices muted should not be interpreted as meaning that I do not find them relevant to understand the history of drug resistance. I would actually argue instead that intellectual and social history can hardly be fully understood without each other. Given the short nature of this work, they were not considered here, but I hope they can be considered in future studies.

Before I finish this introduction with a short summary on how the rest of the dissertation is organized, I would like to clarify my approach to understand what drives historical amnesia of biomedical knowledge. Once I realized there was an earlier history of antimicrobial resistance, and that this history has been overlooked in recent accounts by both biomedical researchers and historians, I wanted to know the drivers of such forgetfulness. Despite my initial enthusiasm, I quickly realized that understanding the reasons behind why we forget about the past, intellectual or other, is actually very fiddly. To put it bluntly, I do not yet know why we forgot about arsenic-resistant syphilis and it would be intellectually dishonest to make strong claims about the issue. Instead, my approach was to survey the historiography of historical amnesia and understand if the arguments made by other authors to explain the forgetfulness about their subject could be plausible to explain the forgetfulness about my own topic. For example, I explored how authors such as Andrew Mendelsohn, Harry Dowling, Ludwick Fleck, Thomas Kuhn, Alfred Crosby, Mark Honigsbaum and Scott Podolsky discussed historical amnesia of scientific and biomedical knowledge, and I argue that their reasoning can be applied, at least partially, to arsenic-resistant

syphilis. However, all these authors are also historical actors and one may certainly gain from localizing them on their social and cultural context. I did not explore this important aspect of historical research and, therefore, I acknowledge that the reader can perceive it as a limitation of my work. I would argue, however, that such analysis should not change the main claims made on how what is known about historical amnesia of biomedical knowledge can help us to understand the historical amnesia of earlier drug resistance. It could perhaps help us to understand why previous authors focused on some factors and not others, but that is an extra layer of complexity.

I also explored the new field of agnotology (study of ignorance) to understand why we do not know what we do not know, and I argue that what is recognised as passive construction of ignorance, can be useful to understand why we have been overlooking the earlier history of drug resistance. I acknowledge all these and other historians below, but I would like to add here that other authors could be considered as well as indeed the field of social memory is a rich one. For example, I did not consider below the arguments made by Paul Ricoeur in *Memory, history, forgetting*, arguably a landmark in the field of social memory. My focus here was limited to our memory regarding biomedical knowledge and I tried, perhaps not always successfully, to direct my attention to the history side of the issue, and less to its philosophy. Therefore, this and other more philosophical works were not considered, but I acknowledge that their perspective could broaden my present views, and it is another aspect that can be considered in future studies.

In summary, this dissertation is organized in three main chapters, with a concluding chapter right after these in which I review the main arguments of this work, together with the evidence used to support my claims. More precisely, in chapter 2 I discuss the first decades of chemotherapy and I

argue that the period that we typically call “antibiotic era” should be broadened. In particular, I revisit the earlier drugs used in the clinic, as well as their social reception, and I analyse the resemblances that these earlier drugs have with later drugs, particularly modern antibiotics. I discuss the very concept of “antibiotic”, and I argue that it is not as fixed and clear as it is typically assumed in the literature of medical history. In chapter 3, I discuss the history of drug resistance, with emphasis on the history of resistance to antimicrobial drugs. I start by discussing the concept of resistance and how it has been changing over time. I then introduce the canonical historiography of antimicrobial resistance that can be found in the literature of medical history, which suggests that such drug resistance is a relatively recent phenomenon. I then introduce and analyse multiple primary sources on arsenic-resistance syphilis from the first decades of the 20th century, which have been overlooked and are missing from the current historiography of drug resistance. The final part of this Chapter is devoted to revisiting and analysing the argument of the historian Christoph Gradmann, one of the very few authors who studied the early history of drug resistance, but surprisingly concluded that antimicrobial resistance was absent from the clinic before the 1940s. In chapter 4, I argue that the neglect and subsequent forgetfulness I unveil here about the earlier history of antimicrobial resistance resembles what is known about historical amnesia of biomedical knowledge more generally. In particular, I discuss the effect of changes in intellectual interest, the contribution of professional authority, how our capacity to remember depends on the usefulness of the knowledge, among other factors. To be clear, I do not think that any of these factors alone can explain the historical amnesia about the origins of antimicrobial resistance. Arguably, it is more plausible that a combination of these factors does.

- Broadening the antibiotic era -

In 1951 Jules Brunel finished his “Antibiosis from Pasteur to Fleming” with the plea:

Men of science should never forget the extraordinary adventure that befell the great American naturalist Louis Agassiz: While studying the habits of a family of fish, the Siluridae, he thought he had discovered something entirely new, but before publishing anything about it, he delved into the literature and found his ‘discovery’ had already been made by a naturalist whose name was... Aristotle!¹⁴

Brunel was a professor of mycology (the study of fungi), not a historian, but he felt compelled to highlight that the idea of antibiosis and the antimicrobial chemotherapy that followed it were not a recent invention as often announced at his time. Brunel claimed that there was nothing fundamentally new about Fleming’s observations. According to him, the original observations on antagonism between microorganisms date back to Pasteur’s time. Moreover, Brunel argued that several studies had been done to explore the potential of natural products derived from microorganisms as therapeutic agents, that other antibiotics were used in the clinic long before Penicillin, and even that attributing to Fleming the discovery of Penicillin itself is problematic.¹⁵

My aim in this chapter is different from Brunel’s. Brunel provided a detailed list of events and authors who had worked on antibiotics and their clinical use before the 1940s to claim that “Fleming is but a link in a long chain of works beginning with none other than Pasteur himself”.

¹⁴ Brunel J (1951) Antibiosis from Pasteur to Fleming. *J Hist Med Allied Sci* 6:287-301.

¹⁵ Brunel did not explicitly criticize Fleming for this historical amnesia but made the following remark: “Why he [Fleming] did not give a full historical summary before reporting his own observations I have no idea”.

He wanted to give credit to those researchers who had contributed to what happened from the 1940s onwards who had been forgotten in later accounts on the history of antibiotics. Like Brunel, I want to argue here that our ideas regarding the periodization of the antibiotic era should be broadened, and that the discoveries related to antibiotic research that started in the 1940s were not as disruptive as often claimed. But my aim in this chapter is not to clarify who “really” discovered the first antibiotic, or when it was first used in the clinic. This is not a tale of precedence. Instead, I want to highlight that the history of antimicrobial chemotherapy is a rich one, and that apparently simple concepts such as “antibiotics” are not as straightforward as often treated in the literature, namely by medical historians.¹⁶ If one wants to understand the history of antibiotic resistance, and antimicrobial resistance more broadly, then one needs to dive into, and understand, the earlier history of antimicrobial chemotherapy, not just the most celebrated events that started in the 1940s. Such a broadening has scarcely been done. This chapter discusses the history of antimicrobial therapy and conveys the idea that there is no obvious conceptual reason to assume that antimicrobial resistance is a recent phenomenon as often claimed. The socio-cultural practices that foster the emergence of drug resistance, to antibiotics or other drugs, were already present in the earlier decades of the 20th century. In the next chapter, I then focus on the history of antimicrobial resistance, namely the earliest and neglected one.

Defining antimicrobial therapy, antimicrobials and antibiotics

To clarify, by antimicrobial therapy here I mean the clinical use of chemical compounds to kill, or inhibit, the growth of microbes (short for microorganisms) that cause disease. It literally

¹⁶ This is certainly not a feature of medical historians only. Defining what is meant by antibiotics is hardly done by authors that tell stories about them. Indeed, Brunel also did not explore the very concept of antibiotic despite exploring the early history of their clinical usage. I will explore their changing meaning in this Chapter.

means anti-microbe treatment with chemicals. There are other forms of “anti-microbe treatment”, which arguably have an interesting history: phage therapy (i.e., use of bacterial viruses to control bacterial growth) or bacteriotherapy (use of bacteria to directly outcompete disease-causing bacteria or prime the host’s immune system against infecting species, the classical example being the use of probiotics).¹⁷ However, these biological (as opposed to chemical) forms of antimicrobial therapy will not be considered below. The same applies to antiserum therapy. Including their history would go beyond the objective of this dissertation. This study is about the unveiling of the early history of drug resistance that so far has been neglected.¹⁸ Therefore, whenever I refer to antimicrobial therapy below, I mean the clinical use of chemical drugs to treat microbial infections, antimicrobial chemotherapy.

Importantly, I will only consider events in which microorganisms were deliberately targeted. This means that microbes had to be considered disease-causing agents at the time, and, therefore, this chapter refers to the history of antimicrobial therapy that started in the late 19th century. The use of antimicrobials by humans is actually thought to be ancient, as suggested by the discovery of traces of tetracyclines in human skeletal remains from ancient Sudanese Nubia and during the Roman occupation of Egypt.¹⁹ Whatever the source of this tetracycline, and the rationale for its

¹⁷ Examples of relevant works include: Fuller R (1992) “History and development of probiotics” in (ed. R. Fuller) *Probiotics. The Scientific basis*, Springer Science + Business Media Dordrecht; Kutchment A (2012) *The Forgotten Cure. The Past and Future of Phage Therapy*. Springer, NY; Podolsky SH (2006) *Pneumonia Before Antibiotics. Therapeutic Evolution and Evaluation in Twentieth Century America*. Johns Hopkins University Press, Baltimore; Wainwright M (1994) Biological Control of Microbial Infections and Cancer in Humans. Historical Use to Future Potential. *Biocontrol Sci Technol* 4:123-131.

¹⁸ While microbes can evolve resistance to phage, bacterio- and antiserum therapies, these phenomena are not as problematic at the bedside as antimicrobial drug resistance (yet, at least). Drug resistance has been the focus of a plethora of works from a wide diversity of players, including microbiologists and biomedical scientists, physicians and historians of medicine. Hence, it is particularly timely to understand its earlier history.

¹⁹ Bassett E, et al (1980) Tetracycline-Labelled Human Bone from Ancient Sudanese Nubia (A.D. 350). *Science* 209:1532-1534. As it has been put recently, “the origin of [this] tetracycline remains a mystery” (Gould 2016, see full reference in Bibliography). An educated guess for the origin of such tetracycline are tetracycline-producing moulds via mould therapy, as the use of moulds in medicine is thought to be ancient.

use, it can safely be concluded that microbes were not actively being targeted. The same can be said about other ancient medical practices, such as the use of the 1000-year-old Anglo-Saxon remedy that has recently been shown powerful against modern, and multi-drug resistant, bacteria.²⁰ This history will not be covered below.

It is remarkable, however, that the vast majority of stories we find about the history of antimicrobial therapy start in the early 1940s, which coincides with the so-called “antibiotic revolution”, or the beginning of the “antibiotic era”, and it is consistent with celebrated narratives such as “[f]ew events in modern medicine have been considered as revolutionary as the advent of the sulfa drugs and antibiotics in the late 1930s and early 1940s”.²¹ Those that mention events from earlier times, such as the first decades of the 20th century, most often do it in a rather cursory way.²² I will address this approach below, and I will argue that current narratives about antimicrobial therapy, namely those that explore it in revolutionary terms, may suffer from what we can call “mis-periodization”. There was nothing truly revolutionary about what was found starting in the late 1930s and early 1940s that had not been found and used in the clinic decades before. The quantity and diversity, rather than the fundamental quality, of the items available for antimicrobial therapy characterizes the later period. I will also argue that describing medical history as a process of change that is punctuated by drastic breaks with the past, the so-called “revolutions”, can be problematic, as it can lead to the neglecting of “pre-

²⁰ Harrison F, et al (2015) A 1,000-Year-Old Antimicrobial Remedy with Antistaphylococcal Activity. *mBio* 6(4):e01129-15.

²¹ Podolsky 2006 (note 17), page 89.

²² Examples include: Aminov RI (2010) A brief history of the antibiotic era: lesson learned and challenges for the future. *Front Microbiol* 1(134)1:7; Rosen W (2017) *Miracle Cure. The Creation of Antibiotics and the Birth of Modern Medicine*. Penguin Books, NY, Budd 2007, Lesch 2007 and Podolsky 2015 (note 5).

revolution” times when one aims to understand “post-revolution” issues. But first, what are antibiotics and when did the “antibiotic era” start?

It is typically assumed that the antibiotic era started in the late 1930s and early 1940s, but to answer the question one needs to explain carefully what antibiotics are; once we do it, the classical periodization gets arguably blurred. It is common to find narratives on antibiotics and their histories that assume the reader knows exactly what antibiotics are, almost as if it is common sense. Indeed, we all have taken antibiotics at some point in our life. But how do we distinguish antibiotics from other antimicrobials? Addressing this question is key to deciding when the “antibiotic era” started, and what is revolutionary about antibiotics when compared to other antimicrobial drugs. The Oxford English Dictionary is useful to understand where the term “antibiotic” comes from. Selman Waksman appears as one of the very first users of the term to describe substances, *with microbial origin*, that inhibit the growth of bacteria and other microorganisms. The interested reader can find a dedicated work on the original definition of antibiotic by Waksman in “What Is an Antibiotic or Antibiotic Substance?”²³ The microbial origin of the substances was emphasised above, as this is often perceived as the defining feature of antibiotics when compared to other antimicrobial compounds, namely those used before the 1940s. It is no coincidence that Waksman is one of the modern founding fathers of antibiotic discovery from microbial cultures,²⁴ and by extension, Waksman is perceived as one of the founding fathers of the antibiotic era. It can be argued that this emphasis on microbial origin is problematic. It excludes, for example, the sulfa drugs used in the 1930s, and the arsenic-based

²³ Waksman SA (1947) What is an Antibiotic or Antibiotic Substance? *Mycologia* 39:565-569.

²⁴ Most famously, Waksman and collaborators isolated streptomycin from actinomycetes, which was effective against tuberculosis and other bacterial infections.

compounds used from the 1910s to the 1940s. It also excludes antimicrobials that have other natural origin. By 1949 Florey was already noting that “there is an increasing tendency to enlarge the scope of the word [“antibiotic”] to include antimicrobial substances derived not only from microbes but from any living source, including plant and even animal tissue”.²⁵

Interestingly, if we look at some the most used antibiotics in the clinic today such cefalexin, amoxicillin, doxycycline, ciprofloxacin, clindamycin, metronidazole, sulfamethoxazole, azithromycin, levofloxacin and methicillin, just to cite a few, these are either semisynthetic or synthetic and, therefore, do not fit under the original definition of antibiotic by Waksman. And yet we still classify all of them as antibiotics. The diagram of Figure 1 is a recently published timeline showing when the main classes of antimicrobial compounds were introduced in the clinic. One aspect that is striking in the timeline regarding the origin of these antimicrobials is that, even if we artificially set the antibiotic era to the late 1930s, we note that twelve out of the thirty six classes of antibiotics introduced in the clinic since then do not have microbial origin, and are labelled here as “synthetic antibiotics”. It is not clear, therefore, that the origin of the compounds is a good descriptor for what clinical antibiotics are, and this aspect is relevant when one aims to understand their history, uses and abuses.

²⁵ Florey HW, et al (1949) *Antibiotics. A Survey of Penicillin, Streptomycin, And Other Antimicrobial Substances from Fungi, Actinomycetes, Bacteria and Plants*. Volumes I and II. Oxford University Press, London. Citation in page 15 of volume I.

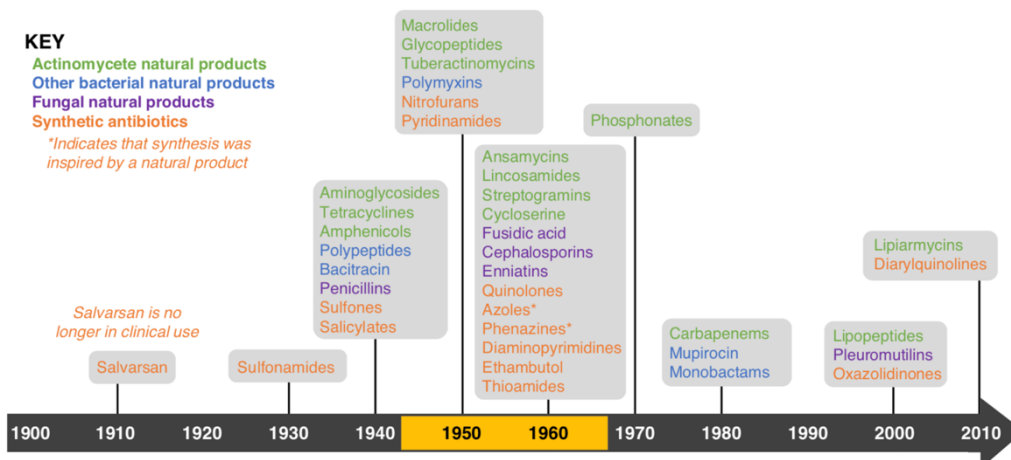


Figure 1: Timeline showing when the classes of antimicrobials, called “antibiotics” here, were introduced in the clinic. Orange-coloured classes are synthetic compounds, green, blue and violet coloured ones have microbial origin. Diagram adapted from Hutching et al., 2019.²⁶

As it will be clear in this dissertation, problems can emerge when we artificially assign one of the known antimicrobials as the “first antibiotic” and start our tales about the antibiotic era from there. Penicillin is by far the favourite choice of most narrators of the history of antimicrobial therapy when it comes to the first antibiotic. The acclaimed discoverer himself, Alexander Fleming, indeed once said, “When I woke up just after dawn on September 28, 1928, I certainly didn’t plan to revolutionize all medicine by discovering the world’s first antibiotic, or bacterial killer. But I suppose that was exactly what I did”.²⁷ Understandably, Fleming characterizes the impact of his discovery to medicine as revolutionary, but it is interesting how he times his discovery and how he defines antibiotics: he discovered Penicillin in 1928 and this, according to him, was the first “bacterial killer”, not the first bacterial killer with microbial origin.²⁸ What Fleming discovered in 1928 was not technically Penicillin. While the original observations that led to its discovery date back to late 1920s indeed, only in the 1940s was Penicillin purified and

²⁶ Hutchings M, et al (2019) Antibiotics: past, present and future. *Curr Opin Microbiol* 51:72-80.

²⁷ Citation in Tan SY, Tatsumura Y (2015) Alexander Fleming (1881-1955): Discoverer of penicillin. *Singapore Med J* 56(7):366-367.

²⁸ Penicillin actually has microbial origin, but that attribute does not seem key to Fleming in this quote.

made available at the bedside. The development of a purification technique was necessary for obtaining the active compound from Penicillin-producing moulds, and that is why the Nobel Prize in Physiology or Medicine of 1945 was awarded jointly to Alexander Fleming, Ernst Chain and Howard Florey “for the discovery of Penicillin and its curative effect in various infectious diseases”, suggesting that it is misleading to think that the discovery occurred in the 1928 alone. After all, only in the 1940s did its curative power become clear. What Fleming effectively found in 1928 was that moulds of the genus *Penicillium* produce an antimicrobial that kills bacterial pathogens. He called it Penicillin, but it was effectively “mould juice”.

If Fleming had chosen the 1940s to date his full discovery, would he be credited as the one who discovered the world’s first “bacterial killer”? By then, there were sulfa drugs that were praised antimicrobial compounds, particularly useful during the WWII.²⁹ Equally important, by then tyrothricin had already been discovered by René Dubos. Indeed, Carol Moberg, biographer of Dubos, claims that “Gramicidin and its less pure form, tyrothricin, were the first antibiotics to be produced commercially and used clinically”,³⁰ and that it was Dubos’ finding that led Florey and Chain to look at Fleming’s experiments published in 1929. Moberg also argues that Dubos’ discovery “represents the first systematic research and development of an antibiotic”. However, it was Fleming who got the Nobel Prize, and it was Fleming who was considered one of the Time 100 Persons of the Century, not Dubos.³¹ Perhaps 1928 was the year when the first

²⁹ Davenport D (2011) The war against bacteria: how were sulphonamide drugs used by Britain during World War II? *J Med Ethics; med hum* 1:4; Lesch 2007 (note 5).

³⁰ Moberg CL (1990) “Friend of the Good Earth: René Dubos (1901–1982)” in (eds. C.L. Moberg & Z.A. Cohn) *Launching the Antibiotic Era. Personal Accounts of the Discovery and Use of the First Antibiotics*, Rockefeller Press, NY. 1990. Citation in page 85.

³¹ In 1939, Gerhard Domagk, credited with the discovery of the first sulfa drug (Prontosil), was also awarded with Nobel Prize in Physiology or Medicine, “for the discovery of the antibacterial effects of prontosil”. In 1952 Selman Waksman got the same distinction but “for his discovery of streptomycin, the first antibiotic effective against tuberculosis”. These are the only Nobel prizes attributed to the discovery of antimicrobial drugs.

“bacterial killer”, as Fleming put it, was first identified, even if in an impure form, and that alone merits the aforementioned distinctions? This idea would imply that there was no antimicrobial therapy before this date, or if there was that it was irrelevant. Were there any antimicrobials used in the clinic before the late 1920s? If there were, in which ways do they differ from Penicillin?

Antimicrobials before Penicillin

It would be surprising if, since Pasteur and Koch first showed that bacteria are disease-causing agents in animals and humans in the late 19th century, there were no attempted to develop antimicrobial compounds to fight bacterial infections until the late 1920s, or if those that existed were all unsuccessful. It would also be surprising if the original idea to look at microbial interactions and microbial products for clinical use would come entirely from a random contamination event, as it happened with Fleming in 1928, when for decades many researchers had been working with microorganisms under less stringent sterility techniques that could easily foster contamination. The search for antimicrobial compounds, of natural or synthetic origin, actually started in the late 19th century, and some of the outcomes of it did get into the clinic and were indeed a success by contemporary accounts, as discussed next.³²

Arguably, the most celebrated antimicrobial used before the 1940s is the synthetic and arsenic-based antimicrobial Salvarsan, discovered by Paul Ehrlich in the early 1900s. It quickly became a clinical tool to target syphilis-causing bacteria specifically. Far from being unpopular, Salvarsan was a true sensation at the time, not just in Germany where it was first developed, but

³² I will not cover disinfectants here as these are typically very toxic to both parasites and host cells, and it quickly became clear they could not be used in the clinic to treat systemic infections. It seems President Donald Trump is not aware of this history; otherwise he would probably not suggest drinking bleach as an approach to treat viral infections such as Covid-19. This earlier history of chemical therapy has been appreciated by medical historians.

all around Europe and North America.³³ Salvarsan and its derivatives were the only specific bactericidal agent for fighting syphilis for more than thirty years until the arrival of Penicillin. By 1910 around 65,000 doses had been administered to over 20,000 patients, “a previously unheard of series before marketing”, and by the end of that year Hoechst was producing 12,000-14,000 doses per day.³⁴ In the UK, for example, it has been claimed that Salvarsan had a profound effect on venereal disease care.³⁵ When discussing the reception of Salvarsan in Britain, Ross and Tomkins note that Salvarsan gained rapid acceptance in the country and that the reception can be characterized by a cautious optimism. They argue that it was mainly the critics of Salvarsan who held unrealistic expectations of the drug and then dismissed it as useless as it was not as good as they pictured it. The majority of the medical opinion was that Salvarsan was both the best treatment and the best prevention for syphilis.³⁶

Patricia Ward arrived at similar conclusions when discussing the American reception of Salvarsan. She noted, for example, that the first results “began almost at once to flood the medical literature, most prominently in Germany, mounting within the first year [1910] more than 1,000 original articles in addition to a number of books and pamphlets”.³⁷ According to Ward, in the United States the appraisal was cautious but hopeful, and favourable reports predominated despite some negative opinions. The author concludes with a very clear and illuminating notion regarding the impact Salvarsan had in the US:

³³ Ross JE, Tomkins M (1997) The British Reception of Salvarsan. *J Hist Med* 52:398-423; Ward PS (1981) The American Reception of Salvarsan. *J Hist Med* 36:44-62; Dowling HF (1973) Comparisons and contrasts between the early arsphenamine and early antibiotic periods. *Bull Hist Med* 47:236-249.

³⁴ Williams KJ (2009) The introduction of ‘chemotherapy’ using arsphenamine – the first magic bullet. *J R Soc Med* 102:343-348.

³⁵ Gelpi A, Tucker JD (2015) The magic bullet hits many targets: Salvarsan impact on UK health systems, 1909-1943. *Sex Transm Infect* 91(1):69-70.

³⁶ Ross and Tomkins 1997 (note 33).

³⁷ Ward 1981 (note 33).

In less than a decade after its initial cautious reception, Salvarsan secured so firm place in American therapeutics that the threat of being without it during World War I prompted action of immeasurable importance to the subsequent growth of the American pharmaceutical industry.³⁸

The account of Harry Dowling regarding a comparison between what he calls “the early arsphenamine and early antibiotic periods”, in which among other topics the author compares the reception of Salvarsan and Penicillin, is also very telling. Dowling explicitly tells us that “[o]verall, the reactions of the public and the medical profession to the advent of an important new drug were practically identical in the two periods”.³⁹ According to the author, as soon as Ehrlich announced the effectiveness of Salvarsan he was “besieged by hundreds of letters a day, innumerable cables and crowds of doctors filling the corridors leading to his office”,⁴⁰ which suggest great enthusiasm about the arrival of this new drug in the medical armamentarium. Importantly for this dissertation, there were times of “mass Salvarsan therapy”, namely during the Great War.⁴¹ Venereal diseases have always been a problem in wartime and the Great War was not an exception.⁴² I will come back to the issue of “mass Salvarsan therapy” in the next chapter, but for now I just want to highlight that such a feature is an important socio-cultural practice that drives the emergence of drug resistance. Famously, mass drug therapy is thought to have driven the emergence of resistance to sulfa drugs during the Second World War,⁴³ and the

³⁸ Ward 1981 (note 33).

³⁹ Dowling 1973 (note 33). Like compound 606, arsphenamine is another name for Salvarsan.

⁴⁰ Dowling 1973 (note 33).

⁴¹ Sequeira JH (1930) The Activation of Syphilis by Treatment. *Lancet* 215:1328-1331.

⁴² Eames JW (1948) The treatment of venereal diseases in the British Army —1898-1948. *J R Army Med Corps* 90: 282-305; Harrison M (1995) The British Army and the Problem of Venereal Disease in France and Egypt during the First World. *Med Hist* 39:133-158; Lane JE (1915) The war and syphilis. *Lancet* 185:724-725; Sequeira JH (1931) Some lessons of the epidemic of venereal disease (1914-1924). *Lancet* 217:57-60.

⁴³ Davenport 2011 and Lesch 2007 (note 29).

link between drug resistance and wartime has been in the spotlight more recently because of the enduring Syria conflict where antimicrobial resistance has been claimed an important problem⁴⁴.

The discoverer of Salvarsan is actually credited as the father of chemotherapy, and the one who coined the idea of “magic bullets” in medicine (i.e., chemicals that can target disease-causing agents such as bacteria specifically). And yet these arsenic-based antimicrobials are not considered as “true” antibiotics despite being “bacterial killers”, to use the expression of Fleming. The timeline presented above in Figure 1 actually does consider arsenicals as synthetic antibiotics, but this view is by far the exception. Salvarsan is mostly neglected in histories of antibiotics. The detailed two-volume dedicated to antibiotic development by Florey and colleagues does not mention Salvarsan for example.⁴⁵ Interestingly, Florey and colleagues do mention other synthetic antimicrobials such as sulfa drugs. Therefore, the fact that Salvarsan does not have a microbial origin is apparently not the reason for its neglect. Perhaps, instead, the reason is that Salvarsan was developed in a period that in the 1940s it was not perceived as “modern” medicine yet? Indeed, by this time Salvarsan became obsolete and Penicillin became the drug of choice for tackling syphilis. Sometimes Salvarsan and other arsenic-based antimicrobials are discussed in the literature, but mainly to highlight their side-effects. Or to note that they were not as efficacious, namely when compared to contemporary antibiotics. One should be careful when comparing therapeutic efficacy and using it as an argument in medical history. As Charles Rosenberg famously contended in his “Therapeutic Revolution”, our perception of therapeutic efficacy changes over time. For example, a therapy was perceived as

⁴⁴ Abbara A, et al. (2018) Antimicrobial resistance in the context of the Syrian conflict: Drivers before and after the onset of conflict and key recommendations. *Int J Infect Dis* 73:1-6; Abbara A, et al. (2018) A summary and appraisal of existing evidence of antimicrobial resistance in the Syrian conflict. *Int J Infect Dis* 75:26-33.

⁴⁵ Florey et al 1949 (note 25).

efficacious before the 19th century when it elicited clear bodily responses, which is clearly a very different way of perceiving therapeutic efficacy when compared to modern views.⁴⁶

It is undeniable that Ehrlich's approach to obtain antimicrobials such as Salvarsan was fundamentally different from Fleming's, Dubos' and their academic followers. But if there is anything revolutionary about the latter is that it fostered the discovery of a plethora of new antimicrobials, while the former did not. Indeed, the discovery of Salvarsan was a relatively isolated event resulting from a brute-force searching method by Ehrlich and his collaborators. Fleming's accidental observations of the late 1920s and Dubos' systematic methodology of the late 1930s can be said to have been critical for the so-called "Golden Age" of antibiotic discovery, as indeed the number of antimicrobials discovered between the 1940s and the 1970s has no parallel in history.⁴⁷ However, equating the 1940s with the beginning of the "antibiotic era" is arguably not straightforward. There was no complete break with the past—a condition that has been considered critical for describing events as revolutionary.⁴⁸ Other antimicrobials were used before, and even the idea of resting on microbial ecology to find antimicrobials was not fundamentally new. One of the most neglected aspects of the history of antimicrobial therapy relates to the initial studies of microbial antagonism and how they led to the discovery of antimicrobials. Some of the original observations suggesting that microbes were sources of

⁴⁶ Rosenberg CE (1977) The Therapeutic Revolution: Medicine, Meaning, and Social Change in Nineteenth-Century America. *Perspect Biol Med* 20(4):485-506. Classical antibiotics with microbial origin also have many side effects. Arguably, one of the most common and now acknowledged side-effects of antibiotics is that they tend to drastically change our microbiome, lead to dysbiosis and ultimately fostering a diverse array of diseases. While modern antibiotics are typically less toxic as some other drugs such as arsenicals, one needs to be careful with how we define "toxicity". Traditionally, it has been thought as the effect of a drug on host tissues. But as we realize that many aspects of our health rely on our microbiome, perhaps the concept of "toxicity" can be broadening as indeed antibiotics are "toxic" to our health more generally.

⁴⁷ See yellow period in Figure 1.

⁴⁸ Porter R (1986) "The scientific revolution: a spoke in the wheel?" in (eds. R Porter & M Teich) *Revolution in History*. Cambridge University Press, Cambridge.

bactericidal compounds were done by Pasteur himself and his group. These observations fostered a plethora of works that eventually led to the discovery of pyocyanase, a compound that was commercially available and used in the clinic for almost 20 years.

A few authors noted that there was a very large number of observations regarding microbial antibiosis (i.e., antagonism between microorganisms) from 1877 onwards, and the first clear observations are attributed to Pasteur and Joubert⁴⁹. Cornil and Babes, the authors of one of the first treatise of bacteriology, put it like this in 1885: “If we were sufficiently advanced in the experimental study of the conflict of bacteria among themselves, most likely the treatment of certain infectious diseases by means of other bacteria would be achieved”.⁵⁰ Soon after the early observations, multiple authors realized that microbes are sources of antibacterial compounds, namely by adding cell-free supernatant (i.e., filtrate) of bacterial cultures to the growth medium of other bacterial species and finding these would stop dividing or would even lyse.⁵¹ Arguably, the rush for finding antibiotics started here, and it is not clear why this period has not been considered by medical historians so far. The search for antibiotics never stopped throughout the 20th century, despite the fact the enthusiasm was not always the same. The case of pyocyanase will briefly be discussed next to highlight that it was a story of success and enthusiasm until it abruptly stopped being such. More generally, the case of pyocyanase helps one to convey that what led to the winding-down of antibiotic research in the early 20th century is still poorly

⁴⁹ Relevant sources: Brunel 1951 (note 14), Florey 1945 (note 25), Florey 1946 and Rolinson 1988. Florey HW (1946) The use of micro-organisms for therapeutic purposes. *Yale J Biol Med* 19(1):101-118; Rolinson GN (1988) From Pasteur to Penicillin – The History of Antibacterial Chemotherapy. *Zbl Bakt Hyg A* 267:307-315.

⁵⁰ Stevenson LG (1958) Antibacterial and Antibiotic Concepts in Early Bacteriological Studies and Ehrlich’s Chemotherapy, in Iago Galston (ed) *The Impact of the Antibiotics on Medicine and Society*, International University Press, NY, page 45.

⁵¹ For example, in 1887, the Swiss Garré claimed that “there is an antagonism caused by the secretion of specific, easily diffusible substances which are inhibitory to the growth of some species but completely ineffective against others”. Citation in Florey 1946 (note 49).

understood, but it does not seem to result of a lack of potential of the compounds discovered by then. Instead, our interest shifted towards other ways of controlling infections, namely antiserum therapy. Notably, the pyocyanase story suggests that the antibiotic era may need to be broadened.

Broadening the antibiotic era

Pyocyanase was introduced into medicine in 1899 by two German physicists, Emmerich and Löw, and the early experiments that explore the potential of using compounds from cultures of *Bacillus pyocyanea* to hamper human pathogens, date back to the 1880s.⁵² Pyocyanase was a preparation from old cultures of *B. pyocyanea*, which was capable of lysing suspensions of multiple bacterial pathogens, and it was extensively used in the therapy of several diseases, particularly diphtheria and meningitis. Figure 2 shows the administration of pyocyanase to a child by Emmerich in 1907. Only in the 1940s was it shown that pyocyanase was most likely a combination of antibiotics because *B. pyocyanea* produces multiple compounds with bactericidal activity.⁵³ While this later research was certainly motivated by the contemporary success of Penicillin, researchers were familiar with the earlier history of pyocyanase and its potential as a chemotherapeutic agent. Indeed, when in 1929 Fleming published his first observations on Penicillin, he compared the bactericidal power of Penicillin against that of pyocyanase: “The bacteriolytic agent, pyocyanase, possesses properties similar to Penicillin in that its heat resistance is the same and it exists in the filtrate of a fluid culture. It resembles Penicillin also in that it acts only on certain microbes”.⁵⁴ It is therefore not clear why he argued the found the first

⁵² This bacterial species that produces pyocyanase is now called *Pseudomonas aeruginosa*. It is a human pathogen, and one of the most problematic multi-drug resistant bacteria nowadays.

⁵³ Hays EE, et al (1945) Antibiotic substances produced by *Pseudomonas aeruginosa*. *J Biol Chem* 159:725-750. Note that here the name of the species was already *P. aeruginosa*, not *B. pyocyanea*.

⁵⁴ Fleming A (1929) On the antibacterial action of cultures of a Penicillium, with special reference to their use in the isolation of *B. influenzae*. *Brit J Exp Path* 10:226-236

“bacterial killer”, as quoted above. Florey too noted that numerous papers confirmed the antibacterial and protective properties of pyocyanase,⁵⁵ being very clear in his 1946 book “The use of micro-organisms for therapeutic purposes”: “There is a very large collection of literature—pharmacological, biochemical, and particularly clinical—at the beginning of this century on this substance. Pyocyanase was used extensively for applications to infected tissues”.⁵⁶



Figure 2: Emmerich administering pyocyanase by an atomizer manipulated by blowing. Illustration adapted from Florey et al., 1949.⁵⁷

Pyocyanase was also not forgotten one year before, when Selman Waksman published the thorough *Microbial Antagonisms and Antibiotic Substances*. There Waksman highlights the “extensive literature” on this antimicrobial substance, its strong bactericidal potential and its mild toxicity. When grouping antibiotic substances according to their toxicity, he put pyocyanase and Penicillin together: “Some substances, as pyocyanase, Penicillin, and streptothricin, are

⁵⁵ For example in Florey et al 1949 (note 25), page 22.

⁵⁶ Florey 1946 (note 49).

⁵⁷ Florey et al, 1949 (note 25).

relatively nontoxic”.⁵⁸ Nowadays, the Oxford English Dictionary defines “pyocyanase” as “an antibiotic preparation, originally thought to be an enzyme, obtained from cultures of the bacterium *Pseudomonas aeruginosa* and formerly used to treat diphtheria and other infections”. But what did contemporaries think about it? Theodor Escherich, the discoverer of the famous laboratory work horse of modern biology, remarked in 1906:

The resumption of these endeavours first became possible when the march of science made known to us a substance which possessed a high bactericidal capacity and at the same time did not harm the tissues as did previously known antiseptics. This material is the bactericidal substance from the autolysis of bacteria, discovered by Emmerich and Löw.⁵⁹

This opinion was widespread. Pyocyanase was commercialised and used in hospitals. In 1913 Dr Sonnenberger published an extensive review on pyocyanase, in which one can find a very clear statement:

The study of pyocyanase as a therapeutic agent is based on exact theoretical considerations. These are backed by clear-cut experiments both *in vitro* and *in vivo*. Its harmlessness within the limits of its usual employment is well established. Its capacity for healing in a large number of diseases has been proved in the clinic. Pyocyanase may be considered an important addition in therapeutics. Its widespread use is recommended within the limits given in this work.⁶⁰

Later, it was even claimed that “[t]he enthusiasm, arguments and perturbations of the pyocyanase era provide a most interesting preliminary and parallel to the story of Penicillin”.⁶¹ Why did it stop being used? Some contemporaries voiced their concern that its quality deteriorated over time, others argued that it was toxic, others argued that it never had been so good as claimed. But

⁵⁸ Waksman SA (1945) *Microbial Antagonisms and Antibiotic Substances*. The Commonwealth Fund, NY.

⁵⁹ Florey 1946 (note 49), page 22.

⁶⁰ Florey et al 1949 (note 25), page 24.

⁶¹ Stevenson 1958 (note 50), page 48.

as Florey noted, “it is difficult to believe from records that pyocyanase was worthless when properly prepared in an active state”.⁶² It would indeed be hard to explain why researchers were trying to isolate the active components of pyocyanase in the 1940s if the consensus was that the clinical value of pyocyanase was an invention. Florey was clear in his conclusion:

There is no question that the work on pyocyanase was the first serious attempt to introduce an antibiotic into medicine. Practically all the ideas and the type of trials which have been conducted for Penicillin were undertaken by the works with pyocyanase... I have even found a thesis from Switzerland written in 1908 in which pyocyanase was used for treating bovine mastitis by infection into the udder in a way exactly similar to that employed more recently using gramicidin and Penicillin.⁶³

Florey also noted that it was of “considerable historical interest” what some researchers, who were working on the bacteria that produce pyocyanase, wrote in 1927:

As bacteriology progressed the number of antagonisms grew. However, instead of studying them with all the care they deserved, attention was turned exclusively to producing anti-sera from the same organisms and gradually therapy by antagonistic micro-organisms was abandoned. To-day we are witnessing a conspicuous revival of this means of therapy.⁶⁴

This shift in intellectual interest is arguably relevant to understanding why antibiotic research slowed down in the first decades of the previous century. One may well wonder why serotherapy was privileged at the time and why “therapy by antagonistic micro-organisms” was revived in the late 1920s. But addressing these questions would go beyond the objectives of this dissertation.⁶⁵ What seems clear from what was discussed above is that there is nothing fundamentally new about the antibiotics introduced in the clinic from the 1940s onwards. It is

⁶² Florey et al 1949 (note 25), page 25.

⁶³ Florey 1946 (note 49).

⁶⁴ Florey et al 1949 (note 25), page 24.

⁶⁵ Podolsky 2006 (note 17), is a detailed work on the transition between serotherapy and what the author calls the “antibiotic revolution” of the 1940s, but he neglects there was antibiotic therapy before serotherapy itself.

also clear that our definition of “antibiotics” changed over time. Initially, they were defined as antibacterial compounds of microbial origin, then antibacterial compounds of natural origin; now any antibacterial compound can be called an antibiotic. If it has synthetic origin, it is a “synthetic antibiotic”. Even their recognised target and specificity are problematic. While antibiotics are widely described as bacteria-specific drugs, many antibiotics are used, for example, against tumours. And some compounds “with microbial origin” actually target other microorganisms other than bacteria such as virus so the original definition of “antibiotic” is problematic at multiple levels. In short, it is safe to say that what we call antibiotics is a mixed bag of drugs. We should recalibrate our narratives if we work on their history and set the 1940s as the beginning of our tales. It can be perceived as arbitrary, and even misleading, depending on the context.

In the next chapter, I discuss the history of antimicrobial resistance, and I argue that it is older than we often assume. The reader may wonder why I have titled it “antimicrobial resistance” (and more generally why I have titled this thesis “The forgotten origins of antimicrobial resistance”) if I am unveiling the neglected history of resistance to Salvarsan, which can be defined as a synthetic antibiotic. Indeed, I have just argued in this chapter that the antibiotic era should be broadened! Could I call this thesis “The forgotten origins of antibiotic resistance”? I could, but it could lead to unnecessary confusion and “antimicrobial resistance” is unmistakably correct. “Antimicrobial resistance” is a more general concept, and indeed it has become the most common term utilised in the literature, namely in the medical literature.

- Antimicrobial resistance before Penicillin -

This chapter is about the history of antimicrobial resistance, with particular focus on the earliest and most neglected one so far. There is a vast literature on the most recent history of antimicrobial resistance, namely the one that emerged after the introduction of Penicillin and modern antibiotics in the clinic, starting in the 1940s. I will not consider this history in detail below because the reader can find excellent works on the topic.⁶⁶ I will, however, refer to this literature to highlight that it does not consider similar phenomena that happened before the introduction of Penicillin in the clinic and, therefore, tend to treat antimicrobial resistance as a relatively new phenomenon that resulted from the recent overuse of antibiotics in the clinic and husbandry. I will argue in the following chapters that this neglect of the earliest history of antimicrobial resistance is, at least partially, a consequence of considering the antimicrobial chemotherapy that started in the 1940s as a revolutionary period.

Those most familiar with this topic will recall that there is some work on the emergence of resistance to sulfa drugs.⁶⁷ While we still know little about the specific conditions that contributed to such resistance, as well as our responses to the problem, it is generally appreciated that resistance to sulfa drugs developed during the World War II because of overuse of these

⁶⁶ Excellent examples include Bud 2008 (note 5), Podolsky 2015 (note 5), Summers 2008 (note 6) and Levy 2002 (note 7).

⁶⁷ Examples include Davenport 2011 and Lesch 2007 (note 29). Davenport convincingly argued that there was free distribution of sulfa drugs during the Second World War, and that both soldiers and civilians were often self-medicated, which are factors that can indeed lead to the emergence of antimicrobial resistance. Lesch also briefly mentions the problem in his dedicated book about sulfa drugs, *The First Miracle Drugs* (note 5).

medicines throughout the conflict, and that it likely fostered our awareness of the potential of antibiotic resistance years later. Therefore, I will not explore this form of resistance in detail, namely because it can hardly be considered the early history of antimicrobial resistance. Instead, the majority of the chapter is about the rise of antimicrobial resistance in the clinic *before* the introduction of sulfa drugs, which may come as a surprise as it has been argued that there is not much to tell.⁶⁸ I overturn this idea in this chapter. In particular, I will argue that Salvarsan-resistant syphilis was perceived as a problem in the first decades of the 20th century and that it stimulated a wealth of research comparable to the one that occurred decades later for more recent antimicrobial resistance. This research, however, is never cited in works about recent drug resistance. In the next chapter, I discuss some possible causes for such forgetfulness and I compare these events with documented events of social amnesia in science and medicine.

Defining antimicrobial resistance

As I have done in the previous chapter, I will start by briefly explaining what I mean by “antimicrobial resistance”, how it compares to other more familiar terms such as “antibiotic resistance” or “drug resistance” and, importantly, how these concepts changed over time. Ultimately, they all result from the same driving process: evolution by natural selection. Interestingly, this realization is not a recent one. Even before knowing proximal causes of drug resistance (i.e., the specific genetic changes and physiological mechanism driving drug resistance), evolutionary principles were already being mobilized among doctors and coresearchers as I will discuss in this section. But multiple ideas were running in parallel.

⁶⁸ The key reference here is Gradmann 2011 (note 6). I will introduce and analyse in detail the argument of the author in this Chapter, namely in the subsection “*Revisiting Gradmann’s argument*”.

Starting with the most general term first, in the context of chemical therapy, drug resistance is defined in the Oxford English Dictionary as “the property of being drug-resistant” and drug-resistant is defined as “resistant to the effect of a drug or drugs”, where “resistant” should be understood here as the property of being “tolerant”, “immune”, or a like quality. The result of this phenomenon is treatment refractoriness. Drug resistance is a general concept; it can be applied to microbes such as bacteria and viruses, macroparasites or cancer cells, for example, “antimicrobial resistance” is drug resistance in microbes (or put differently, resistance to antimicrobial drugs), while “antibiotic resistance” is a more narrow concept as it refers to resistance to antibiotics specifically. As discussed in the previous chapter, the distinction between antimicrobials and antibiotics is often thin, if any, and, therefore, the same applies to the distinction between antimicrobial and antibiotic resistance. However, in recent decades the use of the latter became more common. Podolsky claimed that this transition is consistent with the change from local to global narratives regarding the problem of drug resistance.⁶⁹ I would argue instead that antimicrobial resistance became more common because antibiotics are most often perceived as anti-bacteria compounds and, therefore, “antibiotic resistance” does not include the emergence of resistance in other microbes such as viruses and fungi that later became recognized as equally problematic. Anti-virals were developed and introduced to into the clinic only in the late 20th century, and the first cases of resistance were published in the 1980s.⁷⁰ The same can be said about resistance to anti-fungal drugs.⁷¹ It is reasonable, therefore, that the broadening of the terminology from antibiotic to antimicrobial resistance happened only recently. One does not

⁶⁹ Podolsky 2018 (note 6).

⁷⁰ Burns WH, et al (1982) Isolation and characterization of resistant Herpes simplex virus after acyclovir therapy. *Lancet* 1(8269):421-423; Crumpacker CS, et al (1982) Resistance to antiviral drugs of herpes simplex virus isolated from a patient treated with acyclovir. *N Engl J Med* 306(6):343-346.

⁷¹ White TC, et al (1998) Clinical, Cellular, and Molecular Factors That Contribute to Antifungal Drug Resistance. *Clin Microbiol Rev* 11(2):382-402

need to invoke “global narratives”, even if these do characterize our recent responses to the problem of antimicrobial resistance as Podolsky correctly noted. I will still come back to his work on the evolving responses to antimicrobial resistance below.

In both forms of resistance, the narrow and the broad one, it is now assumed that what becomes drug resistant is the agent that causes disease, be it bacteria, viruses, or other microbes. More precisely, it results from an adaptive process in the parasite population.⁷² While Darwin and Wallace focused on animals and plants to elaborate their theory, the idea that germs could undergo evolution by natural selection is almost as old. In 1883, Kenneth Millican published one of the first works on the topic, *The Evolution of Morbid Germs*, where the author discusses how microbes become virulent from avirulent strains and more generally “*the novo* origin of a disease”.⁷³ Despite being an early account, the author acknowledged that “the general application of the great doctrine of evolution to disease appears to have been more or less distinctly ‘in the air’ for some considerable time”.⁷⁴ Millican’s key idea can be glimpsed in the following passage:

Suppose that, according to the ‘Germ Theory’ of Disease, specific diseases are due to microorganisms, which we may term Bacteria... we must conceive a time when the ancestors of that organism were not yet disease germs. They existed as Bacteria, but were not pathogenous [sic] Bacteria... Suppose by some mischance, one of these ‘indifferent’ germs is transferred from its customary *habitat* in sewer or stagnant pool into the system of

⁷² At the most basic level it simply means a change in the genetic make-up in the population of replicating agents that cause disease, which in this case was driven by a chemical that limits their reproductive success. If this genetic (and therefore heritable) change is adaptive, one calls it evolution by natural selection. It is exactly the same process used by Charles Darwin and Alfred Wallace to explain the formation of new biological species in nature. The evolution of drug resistance is a process of natural selection because, while it is most often driven by human action (and therefore could be thought as a form of artificial selection), we do not directly choose the replicating agents that survive. Instead, individuals with higher reproductive success under drug stress, autonomously take over their population.

⁷³ Millican KW (1883) *The Evolution of Morbid Germs*. London, page 9, italic in the original.

⁷⁴ Millican 1883 (note 73), page 44.

a human or other organised being, what will be the result? Obviously, that will depend upon its power of ‘adjustment to its environment’.⁷⁵

Pasteur himself used microbial evolution to develop his vaccines by basically “evolving virulence” in his laboratory, changing “wild” (fully virulent) germs into attenuated germs. As he clearly put it, “[I]n a matter of 24 hours, bacteria with their rapid rate of ‘successive generation’ could undergo hereditary change – ‘variations’ or ‘progressive modification’ – of the kind that higher organisms ‘require thousands and millions of years to accomplish’”.⁷⁶ More generally, Nancy Tomes claimed that “the germ theory gained stature because of its harmony with the grand outlines of evolutionary thinking in the late nineteenth century”.⁷⁷ This view may come as a surprise given the current distancing between evolutionary biology and the medical school curriculum.⁷⁸ Indeed, it has been convincingly argued that medical doctors and biomedical researches avoid the word “evolution”, namely in the context of antibiotic resistance.⁷⁹ Finding that evolutionary theory was important for the reception and acceptance of the germ theory of disease in the 19th century is interesting and arguably deserves further studies since, as Tomes noted, this aspect did not get much attention from historians.⁷⁷

⁷⁵ Millican 1883 (note 73), page 52, italic in the original.

⁷⁶ Citation in Mendelsohn 2002. Mendelsohn JA (2002) ‘Like All That Lives’ Biology, Medicine and Bacteria in the Age of Pasteur and Koch. *Hist Phil Life Sci* 24:3-36.

⁷⁷ Tomes NJ (1997) American Attitudes toward the Germ Theory of Disease: Phyllis Allen Richmond Revisited. *J Hist Med* 52:17-50. Tomes also argues that physicians found it very appealing the idea that disease-causing microorganisms could be understood in terms of the same evolutionary principles that applied to all forms of life, as it made their thinking more “scientific”.

⁷⁸ Ness RM, Schiffman JD (2003) Evolutionary Biology in the Medical School Curriculum. *BioScience* 53(6):585-587; Hidaka BH, et al (2015) The status of evolutionary medicine education in North American medical schools. *BMC Medical Education* 15(38):1-9.

⁷⁹ Antonovics J, et al (2007) Evolution by Any Other Name: Antibiotic Resistance and Avoidance of the E-Word. *Plos Biol* 5(2):e30.

The recognition that microorganisms could adapt to new conditions fostered early drug and chemotherapy developers to address this feature. Famously, when Ehrlich was developing his “magic bullets” he was after a chemical agent that could achieve sterile cultures of parasites in animals with a single high dose, the famous “therapia magna sterilisans” (i.e., great sterilizing therapy), partially because he was aware that microbes could develop resistance to drugs if they are regularly exposed to sublethal concentrations.⁸⁰ It is thus not surprising that this aspect is considered in the first works devoted to testing Salvarsan in the clinic. For example, in 1911 a monograph reporting what the authors, Dr Fildes and Dr McIntosh from the Bacteriological Laboratory of the London Hospital, call the first “exact and scientific study of the new drug [Salvarsan]” in England, has a dedicated section on “The Acquired Resistance of the Spirochaetes to ‘606’ [i.e., Salvarsan]” in which the authors say that “it is now well known that trypanosomes are endowed with the power of adjusting themselves to deleterious influences” and that “in the case of spirochaetes also these characteristics have been demonstrated”.⁸¹ Importantly, the authors continue their description by noting the following key aspect:

The problem of the possible production of strains of spirochaetes ‘fast’ [i.e., resistant] to ‘606’ is manifestly of the greatest importance, since if such strains become general the therapeutic value of the substance will be much diminished... the method of production of ‘fast’ strains is to expose the organisms to slightly sublethal doses of the drug; the survivors will then acquire an immunity. In practice, when dealing with ‘606’ such strains, if they occur, will be produced by an initial treatment of too slight intensity.⁸¹

Dr James McDonagh (British surgeon and medical writer), too, one year later, made clear in his book *Salvarsan in Syphilis and Allied Diseases*, which reviews the early experience with

⁸⁰ Ehrlich P (1913) On Chemotherapy. *Brit Med J* 2:353-359.

⁸¹ McIntosh J, Fildes P (1911) *Syphilis From the Modern Standpoint*. Edward Arnold, London, page 221. I am not explaining these passages because I believe it is very clear the ideas put forward by the authors, and prefer to cite their own words so that the reader understands the ideas do not result from my interpretation.

Salvarsan at the Lock Hospital: “Salvarsan does not differ from other arsenical compounds in the way that protozoa can acquire an immunity against its continued use”, adding that “in syphilis this is also the case... no doubt the spirochaetes had acquired immunity against arsenic”.⁸²

Changing meanings of drug resistance

Interestingly, Gradmann recently argued that before the 1940s, resistance mainly meant bodily resistance, at least for most physicians.⁸³ And by “bodily resistance” the author means “the organism’s capacity to withstand an infection”. Gradmann used German literature to support his claim (namely what he calls “Germany’s leading handbook of infectious diseases, in 1930”). However, the English literature clearly suggests a richer picture. If we track multiple editions of pharmacology manuals, we find that the term “resistance” was actually barely used before the late 1940s. Other cognate terms such as “tolerance”, “habituation” or even “immunity” were used most often. Importantly, they were used in different contexts simultaneously, which may help to explain, at least partially, the confusion regarding the causes of arsenic-resistant syphilis that I will explore below. For example, *The Manual of Pharmacology*, by Dr Walter Dixon,⁸⁴ a famous textbook at the time, is instructive because we can see how ideas develop, from 1906 (1st edition) to 1936 (8th edition), which is the relevant period for understanding arsenic-resistant syphilis. In the edition of 1906, one can read the passage on “Tolerance and Immunity”,

Some animals and men fail to react to certain drugs in what should represent considerable dose, and this phenomenon is spoken of as tolerance. Tolerance may be either natural or acquired. ... Acquired tolerance is the result of habituation to the drug, and it is frequently very hard to explain.⁸⁵

⁸² McDonagh JER (1912) *Salvarsan in Syphilis and Allied Diseases*. Oxford University Press, London, page 5.

⁸³ Gradmann 2011 (note 6).

⁸⁴ Dixon WE (1906) *A Manual of Pharmacology*, multiple editions. Edward Arnold, London.

⁸⁵ Dixon 1906 (note 84), page 12.

This section was reproduced almost word by word until the 1936 edition (excluding this), and it seems to agree with Gradmann's claim. Importantly, from 1915 onwards, we can find another relevant passage, but in a different section:

Tolerance to arsenic may be acquired by protozoa, such as the spirochaetes of relapsing fever and trypanosomes. It is well known that Ehrlich gradually produced atoxyl-fast [i.e. atoxyl-resistant] strains of trypanosomes which when injected into mice produce trypanosomiasis which atoxyl even in the largest doses failed to influence.⁸⁶

From there, this passage is reproduced word by word until 1936, and only in this last edition there appears a passage linking the two processes. In the section "Action of a Drug", subsection "Acquired Tolerance", after describing the drug tolerance that can emerge in patients, the author adds that "many parasites, especially trypanosomes and spirochaetes, become resistant to organic arsenicals".⁸⁷ In short, in the same book we find different ideas of drug resistance.

Another passage deserves mention here. It is present in all editions of this manual, and indeed in other manuals of pharmacology from other authors.⁸⁸ The passage reads:

There is little doubt that some degree of tolerance to arsenic may be developed by habituation. The peasants in parts of Austrian Tyrol take arsenic to improve their powers of endurance. They are stated to begin with doses varying from one-sixth to one-eighth of a grain, which are gradually increased till four or five grains are taken at a dose.⁸⁹

⁸⁶ Starting on page 379 for the 4th edition of the book.

⁸⁷ Dixon 1936 (i.e. later edition of Dixon 1906, note 84), page 9.

⁸⁸ Example: Goodman L, Gilman A (1941) *The Pharmacological Basis of Therapeutics*, multiple editions. The Macmillan Company, New York.

⁸⁹ Dixon 1906 (note 84), page 13.

Importantly, later manuals of pharmacology, such as the renowned *The Pharmacology Basis of Therapeutics*, stress that “[i]t is important to emphasize that the bacteria, and not the patient, become resistant to the drug”⁹⁰ when referring to the effects of sulfa drugs and that “[t]he microorganism and not the patient becomes refractory to the action of the drug”⁹¹, when referring to the effects of Penicillin. In short, it seems that drug resistance was perceived as both bodily resistance and a property of microorganisms before the 1940s, and the emphasis on each of these varied among authors, contrasting with the view that Gradmann offers in his work.

The same can be concluded from surveying handbooks of skin diseases. For example, the celebrated Whitfield’s *Handbooks of Skin Diseases* notes that “if there is any danger of establishing a refractoriness of the spirochaetal to arsenic compounds, this danger is much more likely to be avoided by the use of high doses at long intervals than by frequent small doses”,⁹² but *Gardiner’s Handbook of Skin Diseases* emphasizes instead that treatment should be varied “according to the condition of the patient and special circumstances, such as the course of the illness, *resistance or intolerance to drugs* already administered, complications, contra-indications, etc”.⁹³ Shortly after we find similar ideas regarding sulfa drugs.⁹⁴ Even by the early 1940s the concept of drug resistance was not stable and fixed. It did not necessarily mean a property of the infecting parasite. The established McLachlan’s *Handbook of Diagnosis & Treatment of Venereal Diseases* notes, for example, that

⁹⁰ Goodman and Gilman 1941 (note 88), page 1282.

⁹¹ Goodman and Gilman 1941 (note 88), page 1334, italic in the original text.

⁹² Whitfield A (1921) *A Handbook of Skin Diseases and Their Treatment*. Edward Arnold, London, page 232.

⁹³ Kinnear J (1939) *Gardiner’s Handbook of Skin Diseases*. E & S Livingstone, London, page 60. The emphasis is mine in the citation.

⁹⁴ Warwick T (1941) *A Handbook on Venereal Diseases*. Faber and Faber LTD, London, page 219.

the possibility of ‘drug fastness’ [i.e., drug resistance] of the infecting organism has to be considered. It is still undecided whether these [refractory] cases are due to true chemo-resistance of the gonococcus [gonorrhoea-causing bacteria] or to some failure of synergic reaction in the tissues of the host.⁹⁵

Similar discussions about the culprit of drug refractoriness, the body or the microorganism, can be found in the dedicated literature on arsenicals, and I will explore these next. But what seems already clear from what was presented above is that there was no major discontinuity between the early and later history of antimicrobial resistance, namely the one Gradmann claims to exist when he explicitly says, “Its [antimicrobial resistance’s] early history is largely discontinuous with later work, and antimicrobial resistance as it evolved from 1900 to 1940 followed other trajectories than those which became relevant after 1940”.⁹⁶ Even in the 21st century there is some confusion about what antimicrobial resistance is, and the idea of the body’s resistance persists.⁹⁷ The history of arsenic-resistant syphilis in particular shows that Gradmann’s claim does not hold. Next I start by discussing some of the key aspects of the history of arsenic-resistant syphilis, which includes Salvarsan-resistant syphilis, and then I introduce and discuss Gradmann’s argument on the early history of drug resistance in detail.

Remembering arsenic-resistant syphilis

In 1932, Dr Drake and Dr Thomson from the Department of Syphilis of King’s College Hospital, published a paper titled “A New Phase in Early Syphilis”, and their first paragraph was very clear regarding what was about to come:

⁹⁵ McLachlan AEW (1944) *Handbook of Diagnosis & Treatment of Venereal Diseases*. E & S Livingstone, Edinburg, page 241.

⁹⁶ Gradmann 2011 (note 6).

⁹⁷ Brookes-Howell, et al (2012) ‘The Body Gets Used to Them’: Patient’s Interpretations of Antibiotic Resistance and the Implications for Containment Strategies. *J Gen Intern Med* 27(7):766-772.

During the past year we have been disturbed by the growing realization that certain cases of early syphilis have not reacted in the former satisfactory way to routine method of treatment which we have been accustomed to employ. The disturbing signs have been in the main the early appearance of gummata of the throat and skin, which prove extremely resistant to all forms of treatment. These recent experiences have prompted us to examine the records of past years to see if any explanation is forthcoming for the unfavourable course which certain early cases of syphilis are now following.⁹⁸

Their final conclusion was equally clear: “The evidence as a whole points to the possibility that a more resistant strain of spirochaete is beginning to make its appearance”. As one may expect, this work promoted discussion among experts. Arguably, the loudest voice came from the eminent British dermatologist Dr James Sequeira, who published multiple comments on that paper. In of them one reads:

We should be grateful to the authors for bringing forward evidence that a more resistant strain of spirochaete [sic] is making its appearance. Some of us have suspected this for some years, and this suspicion has been supported by the steady increase in the minimum doses of arsenic recommended by directors of V.D. [i.e. venereal disease] clinics, and their advocacy of polytherapy in the treatment of syphilis. ... It would appear not unreasonable to suspect that the increasingly wide use of arsenicals is the chief factor in causing the ‘progressive’ increase in arsenic-resistant cases.⁹⁹

In the same year, in “The increase in arsenic-resistant syphilis”, Dr Sequeira clarifies that “[his] reason for bringing this matter before the profession is to have a thorough investigation of the late results of modern syphilotherapy”.¹⁰⁰ And yet, despite the wording used by Dr Drake and Dr Thompson, almost as if their results were unexpected and novel, drug-resistant syphilis was not a new phenomenon by 1932.

⁹⁸ Drake JA, Thomson MS (1932) A New Phase in Early Syphilis. *Br J Dermatol Syph* 44:297-304. Spirochaetes are syphilis-causing bacteria, see figure 3 for a scanning electron micrograph.

⁹⁹ Sequeira JH (1932) Correspondence. A New Phase in Early Syphilis. *Br J Dermatol Syph* 44:520.

¹⁰⁰ Sequeira JH (1932) The increase in arsenic-resistant syphilis. *Lancet* 220:1133-1134.

Indeed, Dr Sequeira had openly campaigned against the treatment regime undertaken for patients with syphilis before. In “Compulsory treatment of venereal disease: A protest” and “The activation of syphilis by treatment”,¹⁰¹ both published in the prestigious *The Lancet*, Dr Sequeira warned that the conditions that promote the emergence of drug resistance—small doses of drugs regularly administered—were “completely fulfilled” at the time, adding that “Klauder [physician-researcher] has shown that repeated small doses of arsenical compounds may produce in animals arsenic-resistant spirochetes [sic], and there is good reason to believe that this obtains in man”. Such discussions were not unique to British medicine. For example, in 1936, the eminent American dermatologist Dr Herman Beerman published a critical review titled “The problem of treatment-resistant syphilis”, in which he cites more than 400 works that discuss the drivers of arsenic-resistant syphilis, namely in Europe and the US, combining laboratory and clinical studies, from the early 1910s to the mid 1930s. As Beerman notes at the start of his extensive literature review, “The problem of syphilis resistant to treatment has been studied with so much interest that to make a survey of the pertinent literature becomes a task of colossal importance”.¹⁰² According to this and other works on the topic, German doctors were the first to report the phenomenon in the early 1920s, then the French, and soon after arsenic-resistant syphilis was being discussed in other countries, namely England and the United States.

The driving factors of such resistance, however, were never fully understood. Experts often debated about the most basic questions, such as, “What happens when an infection becomes drug

¹⁰¹ Sequeira JH (1930a) Compulsory treatment of venereal disease: A protest. *Lancet* 215:159; Sequeira JH (1930) The Activation of Syphilis by Treatment. *Lancet* 215:1328-1331.

¹⁰² Beerman H (1936) The Problem of Treatment-Resistant Syphilis. With Special Reference to Arsphenamine-Resistant Syphilis. Review of the Literature and Experimental Study. *Amer J Syph Gon Ven Dis* 20:165-334.

resistant? Is the change primarily in the host or in the parasite, and what is the nature of the change? What are the factors which conduce to the production of a drug-resistant infection?”, as it was put forward by Dr Warrington Yorke in his “Drug-Resistance” article, which was based on an address delivered to the Medical Society for the Study of Venereal Diseases in 1933.¹⁰³ The author concludes his essay by saying that “[w]hilst a great deal has been written on the question of drug-resistant syphilis, next to nothing exists in the way of precise knowledge of this subject”. By 1942, in one of the last extensive works on the topic, it was concluded that “the problem of the cause of treatment-resistant syphilis is still in a state of flux. There is much evidence suggesting the importance of the host, the drug or the spirochete, or a combination of these in the production of this state”.¹⁰⁴ Indeed, the authors’ own research showed that the parasite could unmistakably cause treatment-resistant syphilis, but they did not discard the relevance of the other factors under some conditions.

From the mid 1940s onwards, Penicillin became the drug of choice to tackle syphilis and, understandingly, its introduction in the clinic led the research on arsenic-resistant syphilis to stop. It was a relatively slow process, as we still find some minor works on this topic in the late 1940s and mid 1950s.¹⁰⁵ Despite the lack of consensus in the field, however, we cannot simply conclude that antimicrobial resistance was “absent from clinical medicine” before 1940 as Gradmann recently claimed.¹⁰⁶ Gradmann apparently missed the large literature on arsenic-resistant syphilis as this suggests that antimicrobial resistance has been present in the clinic since

¹⁰³ Yorke W (1933) Drug-Resistance. *Br J Vener Dis* 9:83-109.

¹⁰⁴ Beerman H, Severac M (1942) The Problem of Treatment-Resistant syphilis. Further Studies on a Treatment-Resistant Strain of *Spirochaeta Pallida*. *J Invest Dermatol* 5:269-282.

¹⁰⁵ For example, Probey TF (1948) Attempt to Produce an Arsenic-Resistant Strain of *Spirochaeta pallida* in Experimental Syphilis. *Public Health Rep* 63:1654-1659; and Rajam RV, Rangiah PN (1955) Treatment-Resistant Syphilis. Short Review and Report of a Case. *Br J Vener Dis* 31:25-29

¹⁰⁶ Gradmann 2011 (note 6).

the beginning of chemotherapy. More specifically, in the same work Gradmann claimed that “no such thing as a strain of *Spirochaeta pallida* to Salvarsan ever turned up”, which is clearly at odds with the above-mentioned literature. I will come back to Gradmann’s arguments below.

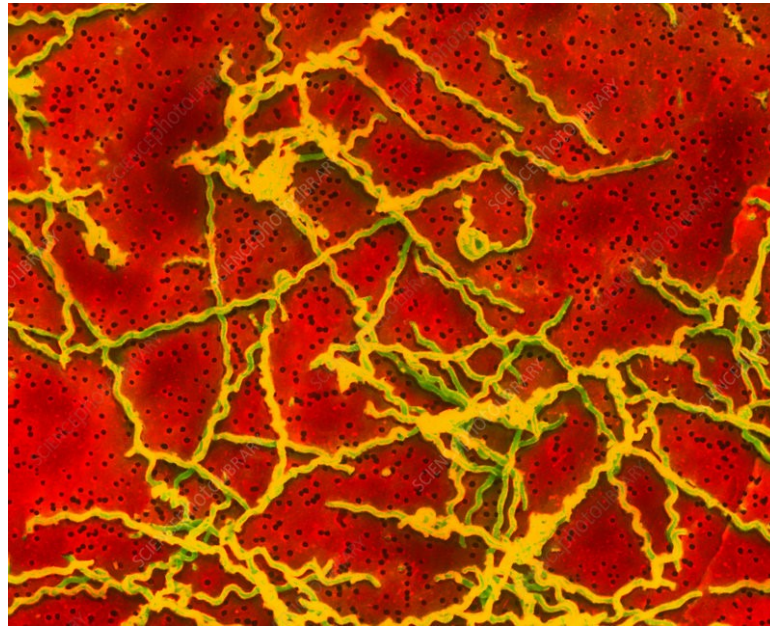


Figure 3: Scanning electron micrograph of spirochete bacteria (yellow). Spirochetes are morphologically very different from the more common rod-or coccoid-shaped bacteria, helping to explain why syphilis-causing microbes were not understood as bacteria initially. From Science Photo Library.

Responding to arsenic-resistant syphilis

In a short review published in 1954, Rajam and Rangiah noted that the practical responses to circumvent treatment-resistance syphilis were basically “raising the arseno-bismuth dose, changing the drug, and non-specific measures such as injections of liver extract and malarial therapy”.¹⁰⁷ Combinatorial drug therapy, namely the combination of arsenicals and bismuth, was itself fostered by the emergence of drug resistance as Downing noted in one of his essays.¹⁰⁸ But

¹⁰⁷ Rajam and Rangiah 1955 (note 105).

¹⁰⁸ Dowling 1973 (note 33).

a more detailed description of the practical responses to drug-resistant syphilis can be found in the extensive review of Dr Beerman of 1936, and these include “changing the preparation to another member of the same group”, “changing the manufacturer’s lot of the same preparation”, “changing the manufacturer’s brand of the same drug”, “changing to another type of antisyphilitic agent”, and nonspecific measures such as “high caloric diet”, “temporary suspension of antisyphilitic treatment”, “elimination of other intercurrent systemic diseases”, “shock therapy with milk”, “gonococcus vaccine, autohemotherapy”, “sodium nucleinate”, “fever induced by malaria”, and “sulphur preparations”.¹⁰⁹

These “responses”, however, are simply forms of local management of treatment-resistant syphilis and clearly not of the same nature than the collective responses that Podolsky explored recently in his “The evolving response to antibiotic resistance”.¹¹⁰ Here Podolsky argues that the changing responses to antibiotic resistance can be grouped in five eras, from 1945 to the present: Era I (1945-1963) is characterized by persistent optimism and relative neglect of the problem; Era II (1963-1981) is characterized by increasing concern after the discovery of horizontal transmission of antimicrobial resistance (i.e., after discovering that bacteria can transfer resistance between strains and species via small chunks of DNA called plasmids); Era III (1981-1992) is characterized by the framing of antimicrobial resistance as a global problem but with little federal attention; Era IV (1992-2013) is characterized by increasing collective attention and funding devoted to solve the problem as observers started to draw attention to the broader economic and national security implications of antimicrobial resistance; and Era V (2013-present) is characterized by framing the problem “As important as climate change”, after the

¹⁰⁹ Beerman 1936 (note 102).

¹¹⁰ Podolsky 2018 (note 6).

pivotal warning by Dame Sally Davies I quoted in the first Chapter of this dissertation (see page 2). Podolsky does not consider what happened before 1945, likely because his working definition of “antibiotic” is consistent with antibacterial compounds used after Penicillin (this included), as indeed his book *The Antibiotic Era* starts in the 1940s.¹¹¹ Either way, in his 2018 essay, the author treats antibiotic resistance and antimicrobial resistance interchangeably¹¹² and, therefore, it is not clear why one should start the narrative in the 1940s.

Interestingly, Podolsky notes that during the first era WHO convened a meeting on antibiotics and antibiotic resistance “but became bogged down on the very laboratory definition of ‘resistance’ and refrained from taking a coordinating, international role concerning surveillance or appropriate use for several decades”. It seems then that this attitude of being “bogged down” resembles those observed for arsenic-resistant syphilis decades before as mentioned above. Discussions about the relative importance of changes in the host, changes in the parasite, and even the quality of the drug itself to explain the observed cases of drug-resistant syphilis prevented any coordinated response in the field, in a way arguably similar to what happened later with antibiotic resistance but on a national, instead of a global, level.

An important consequence of arsenic-resistant syphilis, which can perhaps be labelled as a response to the problem, was the strengthening between the laboratory and the clinic. This aspect is consistent with what we know about late 19th century medicine.¹¹³ In his *Spreading Germs*,

¹¹¹ Podolsky 2015 (note 5).

¹¹² See for example the “Conclusion” section.

¹¹³ Examples include: Bynum WF (1994) *Science and The Practice of Medicine in the Nineteenth Century*. Cambridge University Press, Cambridge; Worboys M (2000) *Spreading Germs. Disease Theories and Medical Practice in Britain, 1865-1900*. Cambridge University Press, Cambridge.

Michael Worboys argues that the link between laboratory and field was “two-way and reciprocal”.¹¹⁴ Indeed, researchers used clinical observations to motivate their laboratory studies, including *in vitro* and *in vivo* experimental models of syphilis. And the results of these studies were used to explain past (and predict future) clinical observations on treatment-resistant syphilis. For example, when in 1924 physician-researcher Dr Joseph Klauder published the first experimental production of arsenic-resistant strains of spirochetes that cause syphilis in rabbits, he motivated his research with the clinical observations that, according to him, “lend support to the existence of drug-fast [i.e. drug-resistant] strains of *Spirochaeta pallida*”, further noting that “the question of an arsenic-fast strain ... is of considerable importance in the practical employment of the arsenicals in the therapy of human syphilis”.¹¹⁵ Additionally, one of the key points in his summary is the following: “Clinical evidence supporting the belief that *Spirochaeta pallida* may develop increased resistance to arsenic is presented”.

Before Klauder and his *in vivo* studies, *in vitro* studies had also been motivated by clinical observations, such as those from Dr Akatsu and Dr Noguchi, who performed systematic studies of how syphilis-causing spirochetes evolve resistance to multiple chemicals, including arsenic, mercurial and iodide compounds. The authors noted that “[i]n syphilis... it had long been suspected that the causative agent of this disease acquires a gradual tolerance to the action of mercurial and iodide preparations” and that “[t]he intermittent form of treatment generally adopted by clinicians, with gradually ascending doses of the medicaments for each course, bears

¹¹⁴ Worboys 2000 (note 113), page 289. Worboys notes for example that the reception of laboratory work on anthrax from 1860s clearly reveals the growing importance of the link between laboratory and field work.

¹¹⁵ Klauder JV (1924) The Experimental Production of an Arsenic Resistant Strain of *Spirochaeta pallida* in Rabbits. *Arch Dermatol Syph* 9:446-458.

sufficient evidence of this assumption”.¹¹⁶ Clinicians, on the other hand, used these and other experimental results as evidence to support and explain their own clinical observations, or even motivate their own clinical studies. Moreover, and as it was mentioned above, the major reviews on the topic, such as Beerman’s in 1936, included both laboratory and clinical studies and how these works motivated each other. Such reciprocal exchange of knowledge is in sharp contrast with Gradmann’s view, according to which early chemotherapy research was characterized by its “increasing distant relationship to clinical medicine”.¹¹⁷

Revisiting Gradmann’s argument

In 2011, Gradmann published a dedicated work on the early history of antimicrobial resistance titled “Magic bullets and moving targets: antibiotic resistance and experimental chemotherapy, 1900-1940”. I briefly mentioned this work already, and here I will explore the key argument(s) of this author in more detail. To clarify, Gradmann uses the term “antibiotic resistance”, but as he clearly puts it, this is used “in its widest sense to include synthetic chemicals, like arsenical and sulfa drugs, as well as naturally occurring substances, such as penicillin and streptomycin”.¹¹⁸ In this work, Gradmann “reconstructs the concept [antibiotic resistance’s] that was put forward by the German immunologist Paul Ehrlich in 1907”, claiming that “resistance was studied by him for other than therapy-related purposes”.

The phenomenon of antibiotic resistance was indeed very important for Ehrlich’s theory of chemoreceptors, contributing to his Nobel Prize award, and certainly it was not clinical antibiotic

¹¹⁶ Akatsu S, Noguchi H (1917) The Drug-Fastness of Spirochetes to Arsenic, Mercurial, And Iodide Compounds in Vitro. *J Exper Med* 25:349-362.

¹¹⁷ Gradmann 2011 (note 6).

¹¹⁸ Gradmann 2011 (note 6).

resistance that motivated these studies, as the author died in 1915, when there was no substantial discussion about clinical arsenic-resistant syphilis yet. The first relevant reports appeared in the early 1920s.¹¹⁹ However, in parallel with this relevant notion, Gradmann also explicitly claims that “[i]t was in the 1940s that antibiotic resistance arose as an object of study for clinical medicine” and that “[t]his approach [using antibiotic resistance to study cell properties] also serves to explain why British and German researchers continued to study the phenomenon of induced resistance in microbes for decades – despite it being absent from clinical medicine”. As noted above, Gradmann argues that the earlier work on antibiotic resistance “is largely discontinuous with later work”. However, all these last claims are clearly at odds with the literature on arsenic-resistant syphilis I discussed in this chapter.

How did Gradmann arrive at such conclusions? His note 6 is particularly instructive as it supports his following idea: “Experimental medicine would not use the term [“antibiotic resistance”] to describe a trait of a microbe before the 1930s”. In note 6 the author says that, “[i]f we take the *Journal of Bacteriology* as an example, the term resistance is fully absent in the 1920s, and in the 1930s it would appear in two different meanings related either bodily or bacterial resistance”. The problem with this rationale is that this journal is not representative of the available journals on clinical microbiology at the time. Indeed, it is hardly classified as a journal of “Experimental medicine”. Medical journals such as *The Lancet* or *NEJM* were not used; nor, given the available drugs at the time, were the arguably more important journals on clinical and experimental syphilology. As Gradmann actually finds that there were “40 years of research [on drug resistance] and a long list of resistances to various chemicals” by the mid

¹¹⁹ For example, Silberstein S (1924) Zur Frage der salvarsanresistenten Lues. *Arch Derm Syph* 147:116-30.

1940s, knowledge lead to his working hypothesis, “antimicrobial resistance as it evolved from 1900 to 1940 followed other trajectories than those which became relevant later on”.

Gradmann then focuses on how Ehrlich used the phenomenon of drug resistance and how those who wanted to challenge his theories targeted this phenomenon, namely Henry Dale who apparently called drug resistance a “wholly mysterious phenomenon”. The vast majority of the literature used on resistance to arsenicals in Gradmann’s essay is from the 1910s, and this period is hardly the correct one to conclude that there was no antimicrobial resistance in the clinic before the 1940s given that in the 1910s Salvarsan had just arrived in the clinic, it was expensive and relatively hard to find.¹²⁰ Therefore, the 1920s and 1930s are arguably the most relevant decades to look for arsenic resistance in the clinic. Importantly, surveying these two decades would be key to support Gradmann’s strong claim according to which “no such thing as a resistant strain of the [sic] *Spirochaeta pallida* to Salvarsan ever turned up”.

Another aspect that Gradmann missed is that, technically, arsenicals such as Salvarsan were not the first antimicrobial drugs used in the clinic. Quinine is arguably the most famous earlier example.¹²¹ And antimicrobial resistance to quinine has been reported since the first decade of the 20th century and during the Great War.¹²² Given the short nature of this dissertation, I do not consider the literature on quinine-resistant malaria, but from the recent work by Da Silva and Benchimol, there was a great interest on the problem in the early 1900s and there is a vast literature on it, namely German literature, which Gradmann tends to explore often. Dedicated

¹²⁰ Dowling 1973, Ross and Tomkins 1997, Ward 1981 (note 33).

¹²¹ Obviously, there are other examples, such as pyocyanase, which I discussed in Chapter 2.

¹²² Da Silva AFC, Benchimol JL (2014) Malaria and Quinine Resistance: A Medical and Scientific Issue between Brazil and Germany (1907–19). *Med Hist* 58:1-26.

studies on quinine resistance actually seem to predate those on arsenic-resistant syphilis. As for arsenicals, resistance to quinine was never fully understood, and it was attributed to changes in the parasite and/or in the body, being driven by mass therapy campaigns.¹²³ Importantly, it was perceived as a very important clinical problem at the time, which challenges the key argument of Gradmann. Clearly, there are far more continuities between the periods pre- and post 1940s when it comes to antibiotic resistance than what Gradmann notes and discusses in his essay.

Despite the problematic conclusions of Gradmann discussed above, at least he surveyed the first decades of the 20th century to understand the early history of antimicrobial resistance. Other medical historians interested in drug resistance simply start their narratives in the 1940s most often.¹²⁴ As far as I can tell, the literature on arsenic-resistant syphilis I introduced and discussed in this chapter has not been documented and analysed by medical historians. Consequently, antimicrobial resistance is perceived as a relatively new phenomenon that emerged in the second half of the 20th century. Why has arsenic-resistant syphilis been forgotten if arsenicals were used in the clinic for more than 30 years and there is no clear rationale to assume that these drugs, and syphilis-causing bacteria, are peculiar when it comes to the evolution of drug resistance? I explore this puzzling historical amnesia in the next chapter.

¹²³ Da Silva and Benchimol 2014 (note 122).

¹²⁴ Examples include: Bud 2008 (note 5), Levy 2002 (note 6), Podolsky 2015 (note 5), Summers 2008 (note 6).

- Historical amnesia of biomedical knowledge -

It has recently been proposed that arsenic compounds such as Salvarsan and derivatives could be used as alternatives to tackle emergent antibiotic-resistant bacteria since these drugs “do not function as conventional antibiotics”.¹²⁵ This medical recommendation is problematic at multiple levels, but one that is related to the topic of this dissertation is that it ignores the potential for arsenic-resistant infections discussed above. At least for this feature, arsenicals do seem to behave as “conventional antibiotics”. Basic understanding of evolution by natural selection should lead to this conclusion, but it is intriguing that arsenic-resistant syphilis has hardly been mentioned in recent literature, both biomedical and historical, namely in works published after the 1940s. This begs the question: Why did we forget the earlier history of antimicrobial resistance, namely arsenic-resistant syphilis?

Historical amnesia is unfortunately not uncommon in biomedical sciences. Even last year, Leslie and colleagues brought to light how forgetting about the risks associated with older drugs can have dramatic consequences to patients in the present. More precisely, the authors show that some of the side-effects of SGLT2 inhibitors (drugs used to lower blood sugar in patients with type 2 diabetes mellitus) were re-discovered in the 21st century, despite being available in 19th- and 20th-century mainstream medical literature.¹²⁶ The result of such forgetfulness is hardly

¹²⁵ Warner WD, Soloway AH (2017) Infections caused by resistant organisms: Could organic arsenic compounds be an effective treatment? *Med Hypotheses* 104:78-79.

¹²⁶ Leslie BR, et al. (2019) Sodium-Glucose Cotransporter-2 Inhibitors: Lack of a Complete History Delays Diagnosis. *Ann Intern Med* 171:421-427.

difficult to appreciate, and it includes avoidable morbidity, mortality and economic costs. Other cases of historical amnesia are known in the context of drug development, as the historian Jeremy Greene highlights in his comment on the work of Leslie and collaborators.¹²⁷ Clearly, biomedical knowledge is not inherently cumulative as often pictured, and as Greene suitably concludes, “[K]nowledge does not just accumulate, it is forgotten and erased all the time”. The task for the medical historian, then, is to unveil the driving forces of such memory and knowledge losses. Below, I discuss some of the social and cultural forces that likely contributed to the neglect of arsenic-resistant syphilis.

Historical amnesia via shifts in intellectual interest and lack of knowledge usefulness

One way to tackle why we forget biomedical knowledge is by addressing a more general question: Why don't we know what we do not know? This is the question that the historian Robert Proctor and the philosopher of science Londa Schiebinger aim to address with the new field of inquiry that they called “agnotology” (etymologically, study of ignorance). Their recently edited book, *Agnotology: The Making and Unmaking of Ignorance*, brings together a set of experts who discuss the causes of absence of knowledge related to a plethora of topics ranging from military secrecy and climate change to female orgasm and to how such absence can be the result of cultural and political forces.¹²⁸ In the introductory chapter of the book, Proctor describes three kinds of ignorance: “ignorance as a *native state* (or resource), ignorance as *lost realm* (or selective choice), and ignorance as a deliberately engineered and *strategic ploy* (or active construction)”.¹²⁹ The last two kinds result from social forces, the first of them being perceived

¹²⁷ Greene JA (2019) Amnesia, Adverse Effects, and the Angel of History. *Ann Inter Med* 171:434-435.

¹²⁸ Proctor RN, Schiebinger L (eds) (2008) *Agnotology: The Making and Unmaking of Ignorance*. Stanford University Press, Stanford.

¹²⁹ Proctor and Schiebinger 2008 (note 128), page 3, italics in the original.

as an inevitable outcome of knowledge acquisition and includes selection processes, inductive reasoning, and cognitive biases. The latter of the two kinds of ignorance is deliberately created and maintained, including, for example, scientific fraud.¹³⁰

Most chapters of the book explore the third kind, active production of ignorance, including the famous strategies employed by the tobacco, asbestos and oil industries to limit the public's understanding of the risks associated with their products. The generation of "doubt" and "controversy" has been part of their strategy to such an extent that the tobacco industry admitted internally that they manufactured two different types of products, cigarettes and doubt.¹³¹ While this form of ignorance is both interesting and relevant to understanding why we do not know what we don't know, I did not find any evidence that can support the idea of active production of ignorance in the context of arsenic-resistant syphilis. There was indeed controversy around the topic, but mainly because the meaning of the problem was not fixed at the time, as I described previously. In contrast to what we find in the context of cigarettes, for example, it is not clear who would benefit from generating controversy regarding drug-resistant syphilis. Nationalism could in theory be a driving factor, as Salvarsan was often called "German poison", namely by the French.¹³² This being said, such an explanatory model is probably not that relevant in this context. German doctors were the first to warn against Salvarsan-resistant syphilis and, therefore, nationalism alone cannot be the source of the controversy.¹³³

¹³⁰ Pinto MF (2019) Scientific ignorance: Probing the limits of scientific research and knowledge production. *Theoria* 34(2):195-211.

¹³¹ Proctor and Schiebinger 2008 (note 128), page 17.

¹³² Gaucher E (1917) Le 606 ou le poison Allemand. *Ann Mal Vener* 12:704-706.

¹³³ For example, Silberstein 1924 (note 119).

The second kind of ignorance that Proctor describes, the one that results from a passive construction, is arguably more useful to understanding why we forgot about arsenic-resistant syphilis. As Proctor put it, “[I]nquiry is always selective”, and the ignorance that results is, therefore, a “product of inattention”.¹³⁴ The chapter by Schiebinger in the aforementioned book emphasizes this type of ignorance, where the author explores the movement, mixing and extension of botanic knowledge between Europe and West Indian colonies.¹³⁵ Schiebinger argues that voyagers imported some kinds of knowledge while others were ignored, and that such selection was driven by multiple factors, ranging from patronage and state policies to what the author calls “moral and professional imperatives”. In particular, Schiebinger argues that knowledge on abortifacients did not travel as effectively from the New World to Europe, partially because colonial enterprises were largely male and men were interested in other types of plants such as medicines that could protect explorers from disease; furthermore, fertility control was against the interests of mercantilist states, which typically fostered growing populations.

The line between apathy and suppression in the context of producing ignorance is not always sharp, but undeniably intellectual interests change over time, and it is not hard to understand how the “antibiotic revolution” led to apathies regarding older therapeutics. Indeed, this is one of the key ideas put forward by Podolsky in his book *Pneumonia Before Antibiotics*. The author argues that the antibiotic therapy emergent in the 1940s made the period roughly between 1900 and 1940 a “relatively forgotten era of therapeutics in America medicine”.¹³⁶ This idea resulted from his own historical work on serotherapy, which according to Podolsky became largely ignored

¹³⁴ Proctor and Schiebinger 2008 (note 128), page 7.

¹³⁵ Proctor and Schiebinger 2008 (note 128), page 149.

¹³⁶ Podolsky 2006 (note 17), page 147.

with the advent of antibiotics in the 1940s. Before these authors, Ludwick Fleck had already stressed the importance of considering shifts in interest when one tries to understand the paths taken, and not taken, in intellectual history. For instance, Fleck asks us to consider if the lack of realism in anatomic illustrations from medieval Islam inevitably reflects poor understanding of human anatomy. The author argues that schematic sign language dominated over realism, partially because it had greater value for them than for us.¹³⁷ I will still return to Fleck below.

The celebrated Harry F. Dowling warned about historical amnesia of biomedical knowledge by specifically comparing the arsenic and the antibiotic periods.¹³⁸ Dowling noted that the usefulness of combined chemotherapy for tackling drug-resistant infections, as well as the phenomena of synergism and antagonism between drugs that had been documented in the arsenic era, had to be “re-discovered” decades later. The author did not fully appreciate that antimicrobial resistance itself had to be re-discovered later as well, but he offered several reasons for the historical amnesia he studied, which are relevant to understanding why we forgot about arsenic-resistant syphilis. First, Dowling noted that trypanosomes and spirochetes were considered very different from bacteria. Indeed, syphilis-causing spirochetes were not even considered bacteria at the time. Related to this important idea, I would add that syphilis was understood as being a very peculiar disease when compared to other infectious diseases.

It is, therefore, not straightforward that doctors and researchers working on other bacterial infections would find it particularly useful to review the literature on syphilis treatment when they came across with antibiotic resistance in the 1940s, for example. As the syphilologist

¹³⁷ Fleck L (1979) *Genesis and Development of a Scientific Fact*. University of Chicago Press, London, page 137.

¹³⁸ Dowling 1973 (note 33).

Charles Dennie clearly put it in 1950, “Whether we like it or not, those in the major divisions of medicine look on us specializing in dermatology and syphilology with ill concealed contempt and regard us as pure externalists”.¹³⁹ In addition to this important notion, Dr Dennie offered another relevant one, according to which the introduction of Penicillin completely changed his field, which affected how other medical specialists looked at it: “Since the advent of Penicillin in the treatment of syphilitic disease, that antibiotic has pierced the heart of the syphilologist and made a field day for the syphilographer. The internist, the surgeon and the obstetrician consider the disease of syphilis of minor importance”. While the disease was not wiped out as those doctors foresaw, and spirochetes acquired resistance to several classes of antibiotics, Penicillin is still effective against syphilis today as Penicillin-resistant syphilis is rare.¹⁴⁰ This again supports the idea of syphilis-causing bacteria being perceived as unusual. In short, the peculiar social and biological nature of syphilis when compared to other infectious diseases likely contributed to amnesia about arsenic-resistance once modern antibiotic therapy began in the 1940s.

Another aspect that Dowling considers relevant to explaining the apparent amnesia associated with the arsenic era is what he calls the practical usefulness of that knowledge. The author says that “the demonstration of a practical use for a concept tends to link together the facts relating to the concept, while those that cannot be tied tend to be ignored”.¹⁴¹ In the context that Dowling explores, combinatorial therapy was understood as “merely a laboratory curiosity”, and hence “accounts of these studies were buried in obscure fine print until most people forgot them altogether”. In a similar way, one could argue that, while it was known that arsenic-resistant

¹³⁹ Dennie CC (1950) The Dying Syphilologist. *Arch Derm Syph* 62:615-621.

¹⁴⁰ Stamm LV (2010) Global Challenge of Antibiotic-Resistant *Treponema pallidum*. *Antimicrob Agents Chemother* 54:583-589.

¹⁴¹ Dowling 1973 (note 33).

syphilis was particularly relevant in Germany and France, as it was relatively rare in Britain and in the United States, many doctors may have perceived it as a curiosity or a mild problem at best. The lack of consensus in the field regarding its ultimate cause probably did not help to changing this idea as well. But even if consensus had existed, even if arsenic-resistant syphilis had become common in Britain and the United States, what would be the practical utility of such knowledge?

There were virtually no alternatives to Salvarsan and derivatives to treat syphilis before the 1940s. This situation contrasts with what happened decades later when pharmaceutical companies like Bayer, which was not involved in the development of “first-generation antibiotics”, focused on drug resistant infections and used the phenomenon to market their own drugs.¹⁴² Given the lack of utility for arsenic-resistant syphilis in the early decades of the 20th century, can one ask, then, if antimicrobial resistance was a scientific “fact”? Pragmatic philosophy, according to which knowledge becomes true when useful, would argue that it was not.¹⁴³ In a similar way, and curiously related to syphilis, Fleck argues in his book *Genesis and Development of a Scientific Fact* that the Wassermann reaction—an antibody test for syphilis—only became a scientific fact once it became useful: “If the relation of the Wassermann reaction to syphilis is a fact, it became a fact only because of its extreme utility owing to the high probability of success in concrete cases. The moment when this decisive turn occurred cannot be accurately determined”¹⁴⁴. The concept of antimicrobial resistance had to be re-discovered by physicians and biomedical researches in the 1940s when they “re-awaked interest in the concept”, to use the expression of Dowling. It can be argued that the level of our expectations

¹⁴² Gradmann C (2016) Re-Inventing Infectious Disease: Antibiotic Resistance and Drug Development at the Bayer Company 1945–80. *Med Hist* 60(20):155-180.

¹⁴³ Meusburger P, Werlen B, Suarsana L, eds (2017) *Knowledge and Action*. Springer Open.

¹⁴⁴ Fleck 1979 (note 137), page 72, italics in the original.

and anxieties for antibiotics and the earlier drugs such as Salvarsan and derivatives was very different. As noted above, the reception of Salvarsan was optimistic but realistic.¹⁴⁵ The arrival of antibiotics in the 1940s, however, made the idea of “miracle drugs” really sink in. Therapy failures were not tolerated as before and, therefore, antimicrobial resistance became an issue of major interest. Antimicrobial resistance became useful for therapeutic narratives, but also for political ones as I will explore below. It was a slow process though, as Podolsky noted.¹⁴⁶

Historical amnesia via professional authority and the reductionistic narrative

In the provocative “Like All That Lives”, the historian Andrew Mendelsohn asks why we forgot about the importance that bacterial variation had for Pasteur. Variable virulence was critical for Pasteur’s attenuation strategy of vaccine development and, indeed, for his germ theory of disease more broadly. Yet historians of science and medicine have instead been assuming the alternative model, according to which a rigid species dogma characterized the beliefs of bacteriologists of the late 19th century. Put differently, and using Mendelsohn’s own words, a “reductive causal equation between germ and disease” has been assumed.¹⁴⁷

Mendelsohn argues not only that these ideas are incorrect but also that it is important to understand where these ideas came from, and why they remained the classical view. He notes that climate, famine and poverty, all understood as key driving factors of health and disease in the pre-germ theory era, were still important in Pasteur’s etiological model, which is in sharp contrast to what we are led to believe. Disease for Pasteur was not an “accident”, as if it resulted

¹⁴⁵ Side-effects and therapeutic failures were likely not that unexpected in the first decades of the 20th century.

¹⁴⁶ Podolsky 2018 (note 6).

¹⁴⁷ Mendelsohn JA (2002) ‘Like All That Lives’ Biology, Medicine and Bacteria in the Age of Pasteur and Koch. *Hist Phil Life Sci* 24:3-36.

from a random encounter between host and parasite, as Owsei Temkin famously put it.¹⁴⁸

Instead, it resulted from a complex process of interactions between host and parasite, a process that implied bacterial adaptation in the evolutionary sense. Why did this view get lost? According to Mendelsohn, “not least because it has the authority of twentieth-century bacteriologists themselves”, including those who valued history of science and medicine, such as Ludwick Fleck and René Dubos. Additionally, Mendelsohn notes that this view agrees with the long-standing criticism of laboratory medicine and especially bacteriology as unduly reductionist. The author also suggests that forgetfulness may be essential for the process of changes in scientific knowledge, an idea previously explored by Thomas Kuhn in his seminal *Structure of Scientific Revolutions*. Kuhn discussed Alfred North Whitehead’s famous quotation “a science that hesitates to forget its founders is lost”, claiming that “instead of forgetting these heroes, scientists have been able to forget or revise their works”.¹⁴⁹ Kuhn argues that the scientific community has an “unhistorical spirit” about the scientific knowledge that came before current paradigms. More specifically, when new “paradigms” emerge, old ones are often forgotten.

Are these ideas useful to grasp why we forgot the earlier history of antimicrobial resistance, namely arsenic-resistant syphilis? Arguably, yes. If the experts on the history of antimicrobial resistance start their narratives in the 1940s, and others even explicitly conclude there was no antimicrobial resistance in the clinic before this date, one can certainly understand why the idea endures as, unless we can detect there is something wrong with the narrative, the idea can easily

¹⁴⁸ Temkin O (1977) “The Scientific Approach to Disease: Specific Entity and Individual Sickness”, in Temkin O, *The double Face of Janus and Other Essays in the History of Medicine*. Johns Hopkins Press, Baltimore.

¹⁴⁹ Kuhn TS (1970) *The Structure of Scientific Revolutions*, 2nd ed. University of Chicago Press, Chicago, page 138.

be accepted.¹⁵⁰ It should be stressed, however, that the main primary sources used in this dissertation were not hidden in rare book rooms or in obscured archives. For example, the reports on arsenic-resistant syphilis cited above appeared in top-tier medical journals such as *The Lancet* and also in dedicated medical literature about syphilology, which one needs to search when exploring the potential for arsenic resistance and the early history of drug resistance more broadly. Moreover, while PubMed (or more precisely, PubMed's predecessor MEDLARS) only began to computerize medical literature in 1963 as Greene notes when trying to explain the amnesia regarding the side effects of some drugs for type 2 diabetes,¹⁵¹ and indeed we find only a few articles on arsenic resistance there, we still find some, but we find multiple works in other standard search engines such as Web of Science and Google Scholar. And obviously, historians cannot just rely on electronic versions of key sources. My point is a simple one: it is not difficult to find primary sources on arsenic-resistant syphilis and one does not need to cherry-pick some of these to make the claim that this was a topic that was discussed among medical professionals. One just needs to surveying the relevant medical literature of the time to appreciate this fact.

Scientists are often scrutinised and criticised by historians and sociologists of science for not being as objective as they think they are. Cultural, political and economic forces pervade intellectual history, independently of the method used to obtain knowledge, be it the scientific method or other and arguably the vast majority of scientists are not familiar with such interplay.

But, to put it bluntly, that is not their expertise and they can hardly be blamed for something they

¹⁵⁰ My insight came from my background as microbiologist, not as a historian. I was not familiar with the literature on arsenic-resistant syphilis, but I was very familiar with how evolution by natural selection works, namely among microorganisms. Therefore, there were only two options: either the early antimicrobial drugs were very peculiar and did not drive the evolution of resistance which alone would be very surprising and would deserve further studies, or they did but researchers did not search for it. A third option, related to the latter one, is that those who searched did not search thoroughly. The sources presented in the last chapter suggest it was a combination of the last two options.

¹⁵¹ Greene 2019 (note 127).

did not learn throughout their education.¹⁵² Historians, on the other hand, like to congratulate themselves for being able to unveil such a complex and intricate web of interactions and for describing the past as it *really* was (unless they are constructivists, obviously). The historians Nancy Tomes and John Warner put it nicely in “Introduction to Special Issue on Rethinking the Reception of the Germ Theory of Disease”, in which one reads:

During the past generation, historians have come to agree that a linear master narrative of the growth of medical practice is not only misleading but dangerous. They have begun to produce a whole host of alternative narratives that incorporate a rich variety of voices, some that give welcome counterpoints not of harmony but dissonance. And yet, while it has become fashionable to congratulate ourselves for having escaped a master narrative, it is when we enter the classroom that we are most inclined to fall back on the comforting structures of a familiar story. Treating the germ theory as capable of acting on its own works too well at streamlining the plot of an exceptionally complex period of medical change for most of us to resist.¹⁵³

The authors are discussing our perceptions about changes in medical practice over time, which may seem disconnected from the main topic of this dissertation, but for the purposes of my argument here, the relevant passage is “[I]t has become fashionable to congratulate ourselves for having escaped a master narrative”. Narratives of therapeutic revolutions have been explored and criticised by many medical historians, famously in the 1960s by Charles Rosenberg, who focused on 19th-century America, arguing that therapeutic efficacy was both locally specific and historically contingent,¹⁵⁴ and the interest on the topic still endures today, as the recently published book titled *Therapeutic Revolutions: Pharmaceuticals and Social Change in the Twentieth Century*, clearly suggests. As the editors of this book put it in introductory chapter,

¹⁵² Certainly, one can wonder if humanities should be integrated in the curriculum of natural sciences, and perhaps they should indeed, but that goes beyond the point. In practice, that typically does not happen.

¹⁵³ Tomes NJ, Warner JH (1997) Introduction to Special Issue on Rethinking the Reception of the Germ Theory of Disease: Comparative Perspective. *J Hist Med* 52:7-16.

¹⁵⁴ Rosenberg 1977 (note 46).

“[N]arratives of revolutionary change in biomedical therapeutics continue to have lasting exploratory power”.¹⁵⁵ Not surprisingly, the book has a chapter on antibiotics, in which the authors (Scott Podolsky and Anne Lie) argue that narratives of antibiotic revolution have been used by academic physicians to bringing their field to the spotlight, and securing more resources to address the issue of a potential post-antibiotic era. As the authors put it, “[T]he sulfa drugs and antibiotics were revolutionary in no small measure because they were promoted as such, bringing into focus the rhetorical, performative impact of the term ‘revolutionary’ itself”.¹⁵⁶ Arguably, economic and political interests helped the mobilization of the “antibiotic revolution” narrative.

As it can be appreciated from the citation above, the authors chose to start their tale in the late 1930s, with sulfa drugs and then antibiotics, and they challenge the narratives on antibiotic revolution that emerged from there. The authors note that “[a]ntibiotics appeared at a moment particularly prone to describing scientific development in revolutionary terms. After all, the phrase ‘scientific revolution’ has only recently entered common use after Alexandre Koyre gave it broader visibility in 1939”.¹⁵⁷ This idea is actually a very convenient one for their argument. However, and as I argued in previous chapters, it can be problematic to start narratives on the antibiotic era in the late 1930s and early 1940s, namely when we discuss narratives of antibiotic revolution. The reception of the antimicrobials before this period was not perceived in less revolutionary terms (even if earlier commentators did not use the term). My point here is not to criticise their leading argument, as it seems a valid, and valuable, one. But as experts in the field, if they choose to explore narratives on antibiotic revolution—even if to challenge them—and start

¹⁵⁵ Greene JA, Condrau F, Watkins ES (eds) (2016) *Therapeutic Revolutions: Pharmaceutical and Social Change in the Twentieth Century*. The University of Chicago Press, London, page 2.

¹⁵⁶ Greene et al 2016 (note 155), page 34.

¹⁵⁷ Greene et al 2016 (note 155), page 21.

their tales later in the century, their professional authority arguably contributes to the historical amnesia of what came before. Incidentally, the authors are reenforcing the idea that, if there was an antibiotic revolution, such revolution happened in the 1940s.

In *Silencing the Past*, the historian Michael-Rolph Trouillot argues that there are four moments in historical production: fact generation, fact assembly, fact retrieval and finally retrospective significance.¹⁵⁸ According to Trouillot, silences can emerge in any of these moments. Arguably, the retrieval of facts for historical narratives (Trouillot's third moment) depends on what historians, professional or other, find interesting and relevant for their contemporary concerns. As Podolsky and Lie put it in the context of antibiotic revolution narratives, "We do not intend here to focus on the veracity of past or current utopias or dystopias, or whether they have been hyperbolic or unnecessarily glum".¹⁵⁹ By selecting a starting period for their narrative, the authors unintentionally silence the earlier history of the antibiotic era, including the one related to antimicrobial resistance. I have used Podolsky and Lie as an example, but the same applies to other medical historians of antibiotics and antibiotic resistance who place their starting narratives in the 1940s. If we consider Proctor's types of producing ignorance discussed above, this choice can be viewed as a form of passive construction of ignorance.

Additionally, and perhaps comparable with Mendelsohn's second reason to explain the historical amnesia he identified and discussed in "Like All That Lives", according to which such amnesia agrees with the long-standing criticism of laboratory medicine excessively reductionist, forgetting about arsenic-resistant syphilis concurs with the long-standing idea of an "antibiotic

¹⁵⁸ Trouillot MR (1995) *Silencing the Past. Power and the Production of History*. Beacon Press, Boston, page 26.

¹⁵⁹ Greene et al 2016 (note 155), page 20.

era” that started in the 1940s, which was a radical break with past treatment regimes. Arguably, this is a reductionist view as well, as it misses the fact that the history of antimicrobial chemotherapy is older, and richer, than that version.¹⁶⁰ Revolutionary narratives foster breaks with the past, which arguably leads to forgetting about inevitable continuities.

Historical amnesia and pandemics

As I write this dissertation the world is grappling with the most important pandemic in recent history. More precisely, at the time I am writing, almost 20 million people have been infected by the SARS-coV-2 virus. More than 700 thousand have already died in more than 200 different countries and territories around the world. These numbers will certainly increase during the next few months, perhaps even during years, depending on multiple factors, ranging from the availability of effective therapies such as vaccines and/or antivirals, to public health measures and our ability to cope with them in different geographies, as well as our travel plans between places with different prevalence of this disease. These events challenge some of the often-celebrated narratives from physicians, biomedical researchers and public health authorities according to which infectious diseases have been by and large conquered and are things of the past. While my dissertation is not about pandemics and the social struggles that emerge from them, I find it is difficult to reflect about historical amnesia of biomedical knowledge as I am doing here, without thinking about the interplay between historical amnesia and pandemics, and

¹⁶⁰ Regarding Mendelsohn’s idea that forgetfulness may be “essential for the process of change in science” following the Kuhnian narrative, I would not describe it as “essential” as if that was the case there would be no change in science without forgetfulness, and that is hardly true. I would argue instead that forgetfulness can influence the process of change in science, namely its pace. This being said, while I understand the connection that Mendelsohn is trying to make here, I believe that Kuhn was thinking about amnesia between paradigms and as I already argued above, arsenic drugs and microbial antibiotics are hardly part of two distinct paradigms in the history of therapeutics. Therefore, it seems to me that Mendelsohn and Kuhn used the concept of “forgetting” differently, and it is not clear that Kuhn’s view is particularly relevant to understand why we forgot about the views of Pasteur on bacterial variance, which was Mendelsohn’s aim in his paper.

to consider if it can affect our present health crisis. Moreover, links between historical amnesia and pandemics may be useful to understand why we have forgotten arsenic-resistant syphilis.

Arguably, the pandemic that may have more to contribute to this topic is the influenza of 1918, also known as the Spanish Flu. Importantly for my purposes here, it is also known as the “Forgotten Pandemic”, and recently some authors have explored such historical amnesia. For example, Alfred Crosby focused on what happened in the United States in his *America’s Forgotten Pandemic: The Influenza of 1918*, while Mark Honigsbaum explored the British case in *Living with Enza: The Forgotten Story of Britain and the Great Flu Pandemic of 1918*. In a way reminiscent to Crosby, Honigsbaum called it “Britain’s Forgotten Pandemic”. How did these authors explain the forgetfulness about this major event? And what exactly was forgotten? For some context about its dimension first, the 1918 pandemic is thought to have infected five hundred million people and killed between twenty and fifty million of these. As Crosby highlights, “Nothing else—no infection, no war, no famine—has ever killed so many in as short a period”.¹⁶¹ And yet, we find few social allusions to the event while we have, for example, many official monuments and other art forms, as well as books, about the war that was taking place at the time (Figure 4). It is hard to understand why an event with such a human impact was forgotten, namely when compared to other pandemics.

Crosby argues that the Spanish Flu was not perceived as particularly important at the time, which may explain why it did not become afterwards, and offers specific explanations for such lack of importance. First, the author notes that major epidemics were still in living memory, so the 1918

¹⁶¹ Crosby AW (1989) *America’s Forgotten Pandemic: The Influenza of 1918*. Second edition. Cambridge University Press, Cambridge, page 311.

pandemic was about degree, not kind. Importantly, it was “hidden” by the Great War, which was taking place in parallel. As Crosby puts it, “[T]he war was very distracting” and perhaps, as he notes, people may have thought of the flu as simply part of the war. Moreover, Crosby argues that the influenza pandemic of 1918 was very quick and did not have a major equivalent later on. Put differently, it was a singular experience. This aspect may change with the present Covid-19 pandemic, and I will come back to it below. Finally, the author argues that the Spanish Flu did not kill nobody famous as it targeted mainly young adults and, understandably, these are not often in positions of great power and authority. After surveying personal accounts like autobiographies, Crosby noted that individuals actually remembered the event, perceiving it as one of their most influential life experiences. However, the amnesia was at a different level, “on the level of organizations and institutions—the level of collectives”.¹⁶²

Honigsbaum took a slightly different tack, but some of his conclusions were arguably similar to Crosby’s. The author focused mainly on ordinary people and doctors, including also the testimony of survivors. He highlighted, for example, that most deaths occurred in the private space, namely in people’s homes and, therefore, they did not get into public view. But for Honigsbaum, as for Crosby, the war “overshadowed” the pandemic. In particular, the second wave, which was the deadliest, coincided with the Great War’s armistice and, therefore, ran alongside peace celebrations. Before this date, news about the pandemic and its spreading had deliberately been censored, namely in Allied newspapers, the rationale being fear that this information could affect national morale and, therefore, could be detrimental to win the war. This is actually the reason why the 1918 influenza pandemic is known as the Spanish Flu, and it

¹⁶² Crosby 1989 (note 161), page 323.

is a prime example of Proctor's active production of ignorance. Spain, being neutral during the conflict, did not try to hide the pandemic as some of the countries at war did.¹⁶³ Moreover, Honigsbaum notes that the 1918 flu pandemic was short-lived and with an impact that cut across social, sexual and ethnic lines. This aspect, he argued, prevented the Spanish Flu from becoming a vehicle for stigma. The death itself associated with it was not that shocking, at least when compared to other recent pandemics such as AIDS. Finally, arguably important, the author also noted that it is hardly possible to imagine death on such a large scale.

While the ideas offered by these authors are reasonable, the reality is that we do not know why we forgot about this pandemic, namely when compared to other impactful health crisis. Indeed, Crosby himself notes, he is simply offering a "speculation".¹⁶⁴ I would argue that, when historical amnesia is not actively created and deliberately maintained as we find in Proctor's active production of ignorance, lack of interest is the major driver of forgetfulness. Crosby and Honigsbaum blame the war as the focus of our attention at the time. But then we have to ask a different question: What factors drive our interest and attention? What do we consider relevant to remember? Clearly, in the biomedical and public health context, at least, it is not morbidity and mortality alone as for these aspects the 1918 influenza pandemic was not matched by wars and pandemics. These questions hardly have universal answers and will likely change over time and space. It can be said that, after four years of a dramatic war, its ending can understandably dominate people's attention and focus. And as Honigsbaum notes, it is hardly possible to image the degree of death that the Spanish Flu generated, namely when death and misery had been the

¹⁶³ Honigsbaum M (2009) *Living with Enza: The Forgotten Story of Britain and the Great Flu Pandemic of 1918*. Macmillan, New York.

¹⁶⁴ Crosby 1989 (note 161), page 319.

norm for so long. Irrespective of the staggering numbers associated with it, therefore, the fact that this pandemic did not get the attention of contemporaries is perhaps not a major puzzle. This said, it seems clear that what we choose to celebrate, namely in the context of pandemics, is not uniquely dependent on the impact that the event had for contemporaries.



Figure 4: Edward Munch's 'Self-Portrait with the Spanish Flu', considered one of the few art pieces devoted to this disease. Accordingly, the Spanish flu has been called the “forgotten pandemic”. From the Wellcome Collection: <https://wellcomecollection.org/articles/W7TfGRAAAP5F0eKS>

In a way, the Spanish Flu reminded observers that the celebrated biomedical knowledge of the time, the availability of a germ theory and the identification of multiple etiological agents of infectious disease, were not as valuable as pictured then, and after. It indeed illustrated the limitations of biomedical knowledge of its time, as Covid-19 is doing one hundred years later. Why would one want to celebrate such inaccurate (and arguably naïve) hopes regarding the potential of biomedical knowledge? Perhaps one of the best lessons we can take from the

Spanish Flu is that it is not just our knowledge about disease that changes over time. The potential for acquiring disease, and the emergence of new diseases, changes as well.

We forgot this very basic natural fact before, and it is not clear at the present that the Covid-19 pandemic will affect these dynamics. In the last few months there has been a plethora of works from historians and biomedical researches surveying the records on the Spanish Flu looking for lessons that can be useful today. When we survey the Spanish Flu and realize there were several occasions when mass gatherings undeniably had a major impact on the spread of the disease. We can certainly use this past reality to inform the public. These are real, and relevant, examples of the past that can arguably fly easier with lay people, certainly better than predictions from mathematical models and explanations from science experts that often do not tune their language accordingly, as we have seen in the recent months. Why we forget this and other relevant lessons from the past and prefer to focus our attention on the development of new biomedical knowledge is hardly easy to grasp. What is clear is that it is not something new. Combining history and science could be more effective than the latter alone, namely because, as it has already been argued, “History can make science better”.¹⁶⁵ Historical accounts of past research and research practices may contain valuable lessons that can be applied by scientists in the present. Moreover, it can be argued that the social, cultural and political forces that helped to drive science in the past, can also help to better contextualize current scientific endeavours.

Why did we forget about arsenic-resistant syphilis?

When exploring the history of the germ theory of disease, Tomes and Warner have said that,

¹⁶⁵ Casadevall A, Fang FC (2015) (A)Historical Science. *Infect Immun* 83(12):4460-4464.

[e]ven when the germ theory receives the revisionist scrutiny it merits, freshly reconfigured and historicized, it is likely to retain the status of an icon both in population understandings of the medical past and in the way historians construct their accounts of medical history. It is partly for that reason that as historians of medicine we should all care about periodically tacking it up on the wall, standing back, and asking what it means to us. Icons, after all, are not meant to be passively revered, not we can understand them by nodding sagely to express our recognition; their multiple meanings become accessible through contemplation.¹⁶⁶

The same can be said about antibiotics, and the antibiotic era more generally. Indeed, the iconic status that antibiotics and the antibiotic era have in medical therapy is hardly lower than the one that the germ theory has in the context of medical theory. We may need to take them up from the wall periodically and ask if we have been missing something about their history and if that forgotten knowledge affects our current views about them.

So, why did we forget about arsenic-resistant syphilis? It is very clear we did forget about this earlier history of antimicrobial resistance, and this is unexpected given the interest on the topic for the last few decades. Unsurprisingly, societies tend to keep poor records about why they do not think something is important, and this is a challenge for the historian. This can be thought as a general rule of thumb, which applies to arsenic-resistant syphilis. As I have done in this chapter, it can be argued that there were likely multiple and diverse driving factors of the historical amnesia about arsenic-resistant syphilis, ranging from the singularity of syphilis and its etiologic agent when compared to other infectious diseases and bacterial species, to the fact that framing antimicrobial resistance as a relatively recent phenomenon has had the support of the experts of the field, over and over, to the lack of practical utility that knowledge had for

¹⁶⁶ Tomes and Warner 1997 (note 153).

contemporaries. It is hardly possible to rank all these factors by their explanatory power given the present limited evidence of their relevance. I do think, however, that revolutionary narratives have great potential to lead to forgetfulness about what came before. With such narratives, what is remembered is typically the drastic changes, not the continuities.

Our historical amnesia about arsenic-resistant syphilis is also consistent with the more general idea that the first few decades of the 20th century are a “relatively forgotten era of therapeutics”, as put forward by Podolsky.¹⁶⁷ Clearly, the advent of antibiotics overshadowed what came right before them, namely the earlier antimicrobials and the evolution of resistance to them. This idea then begs a question: Which other issues apart from drug resistance did we forget and overlook from this time period? Importantly, can that history repeat itself?

¹⁶⁷ Podolsky 2006 (note 17), page 3.

- Conclusions -

In 1945, Fleming concluded his Nobel Prize acceptance speech with a cautionary tale for which he has been celebrated as a visionary for predicting the rise of antibiotic resistance:

I would like to sound one note of warning. Penicillin is to all intents and purposes non-poisonous so there is no need to worry about giving an overdose to the patient. There may be a danger, though, in underdose. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.

The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr. X has a sore throat. He buys some penicillin and gives himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X's death? Why Mr. X whose neglect use of penicillin changed the nature of the microbe. Moral: If you use penicillin, use enough.¹⁶⁸

We now know that Fleming's musings are actually an oversimplification. Not only underdoses can drive the evolution of antibiotic resistance, but also overdoses do it as well. Indeed, the commonly held myth of completing antibiotic courses has recently been challenged.¹⁶⁹ If we understand antibiotics and similar drugs as selective pressures for bacterial populations, as

¹⁶⁸ Fleming A (1964) Penicillin. Nobel Lectures, Physiology or Medicine 1942–1962. Elsevier Publishing Company, Amsterdam.

¹⁶⁹ Examples include: Read AF, et al (2011) The evolution of drug resistance and the curious orthodoxy of aggressive chemotherapy. *Proc Natl Acad Sci USA* 108: 10871–10877; Huijben S, et al (2013) Aggressive Chemotherapy and the Selection of Drug Resistant Pathogens. *PLoS Pathogens* 11(11): e1005301; Kouyos R, et al (2014) The path of least resistance: aggressive or moderate treatment? *Proc Royal Soc B*:281:20140566; Dar T, Read AF (2016) Does high-dose antimicrobial chemotherapy prevent the evolution of resistance? *PloS Comput Biol* 12:e1004689.

indeed they are, then the guiding principle should be to impose no more selection than is absolutely necessary. The puzzling aspect with relevance for the topic of this dissertation is picturing Fleming as a visionary for predicting a post-antibiotic era. The same can be said about framing René Dubois as the harbinger of antibiotic resistance.¹⁷⁰ Understandably, their personal experience gave them the “insight” for such emergency to come, but medical history could have been used instead (or in addition to), and it was not. More than thirty years before, in 1911, Dr Fildes and Dr McIntosh conclude their monograph on the first clinical studies with Salvarsan undertaken in England, with a very similar warning:

The problem of the possible production of strains of spirochaetes “fast” [i.e., resistant] to “606” [i.e., Salvarsan] is manifestly of the greatest importance, since if such strains become general the therapeutic value of the substance will be much diminished.

The method of production of “fast” strains is to expose the organisms to slightly sublethal doses of the drug; the survivors will then acquire an immunity. In practice, when dealing with “606” such strains, if they occur, will be produced by an initial treatment of too slight intensity. We have observed two cases in which there is reason to suppose the spirochaetes have become to some extent “fast” to “606”... if Ehrlich’s recommendation [to carry the initial course with a maximum severity] is not carried out such cases will become frequent and “606” will then not be of its present value.¹⁷¹

And less than twenty years later, Dr Sequeira remembers the abovementioned authors when voicing his concerns from the very same London hospital:

The warnings of these [Fildes and McIntosh] writers have been amply justified. The conditions they foreshadowed have been completely fulfilled. For a long period, it has been the custom to treat syphilis by small doses of arsenicals repeatedly administered.¹⁷²

¹⁷⁰ Moberg 1999 (note 7).

¹⁷¹ McIntosh and Fildes 1911 (note 81), page 221.

¹⁷² Sequeira 1930 (note 41).

Curiously, in the same essay, Dr Sequeira also explicitly says that “our 20 years’ experience of Salvarsan therapy has resulted in agreement upon one point—that it is impossible to rely upon arsenicals alone to effect a cure”, which sharply contrasts with the optimism that prevailed when Salvarsan was initially introduced in the clinic as this observer tell us:

Hardly at any time in the history of modern medicine has there existed a more intense excitement and a more absorbing interest among the medical fraternity than at present. One of the greatest scourges of humanity—perhaps the most insidious and cruel of all, since it so often places its victims beyond the pale of human sympathy, to be loathed rather than pitied—is on the point of being eradicated.¹⁷³

Indeed, the drug Salvarsan was pictured as the first “magic bullet” by its discoverer Paul Ehrlich and others after him. The intriguing aspect here is that despite the realisation of Dr Sequeira, decades later sulfa drugs were perceived as “miracle drugs”.¹⁷⁴ And, shortly after, Penicillin and modern antibiotics as well.¹⁷⁵ What has changed?

As Allan Brandt superbly illustrates in his *No Magic Bullet*, wonder drugs cannot fight the social and cultural determinants of infections,¹⁷⁶ even if they help to control their etiologic agents temporarily. That is true for Salvarsan, Penicillin, and it can hardly be different for any other wonder drug. This aspect has been fully appreciated by medical historians and it would be redundant to cover it here. However, despite this realization, we still treat modern antibiotics differently.¹⁷⁷ Their singularity in our imaginary is such that we have constructed an “era” for

¹⁷³Schweitzer H (1910) Ehrlich’s chemotherapy: a new science. *Science* 32:809-823.

¹⁷⁴ Lesch 2007 (note 5).

¹⁷⁵ Budd 2007 (note 5).

¹⁷⁶ Brandt AM (1987) *No Magic Bullet. A Social History of Venereal Disease in the United States Since 1880*. Oxford University Press, Oxford.

¹⁷⁷ I am using “antibiotics” here in the conventional sense, as defined as antibacterial compounds with natural—typically microbial—origin. As I discussed in chapter 2, this definition has changed over time.

these more recent drugs, leaving outside the antibacterial drugs that came before them. We now have many narratives about a possible “post-antibiotic era” that rest on an anticipatory logic of a future emergency to come, and these have also been addressed by medical historians.¹⁷⁸ As mentioned above, such apocalyptic rhetoric can be understood as a tactic for securing further research funding, but it is undeniable that antimicrobial resistance needs to be tackled, as it is indeed an important public health concern worldwide. It remains to be shown, however, if we are using the most sensible approach to addressing the problem.

My main intervention in this dissertation is a rather simple one: What we call antibiotics, the drugs that are pictured as having revolutionised modern medicine, are the descendants of other pure, or impure, substances that shared many of the same properties, namely when it comes to tackling infectious diseases. All these chemical compounds seem to have driven similar response in our imaginary—that we can easily conquer infectious diseases—and in the microbes themselves, in which they foster the evolution of antimicrobial resistance. As microbial biology, and history, clearly have shown, bacteria and other microbes can quickly evolve resistance to drugs that negatively affect their reproductive success. Yet our main approach to addressing the problem of drug resistance remains the same over time: fostering the developing of new antimicrobials.¹⁷⁹ When these emerge, the older ones are forgotten, along with the consequences of their use. After a brief period of optimism, the cycle repeats again. How many more of these cycles do we have to undertake to appreciate fully that we need a fundamentally new approach to dealing with disease-causing microbes? It is not my aim here to address this question but instead to highlight

¹⁷⁸ For example, Podolsky 2018 (note 6).

¹⁷⁹ Podolsky 2018 (note 6). Podolsky argues that most attention and funding has been devoted to increasing the supply of antibiotics, namely by stimulating pharma industry with “push” and “pull” mechanisms.

some lessons of the past. An important lesson from the past is that antimicrobial resistance driven by human action is older than we thought and that, unexpectedly, we forgot about it.

I argued in this dissertation that the “antibiotic era” should be broadened. Other chemical compounds were used in the clinic before the introduction of Penicillin in the 1940s, and it is not clear from the biological, and the social, responses they elicited, why they should be left out. It is not surprising for the medical historian that some of the founding figures of the modern antibiotic era picture their contribution as revolutionary and forget, intentionally or not, about the continuities from their recent past. As Brunel remarked, “Why he [Fleming] did not give a full historical summary before reporting his own observations I have no idea”.¹⁸⁰ This being said, it would be misleading to claim that this is a general feature of biomedical researchers. Indeed, if we compare the behaviour of Fleming with Florey, for example, these are individuals who lived at the same time in the Western civilization, had the same profession, and were equally successful at it. They even shared the same Nobel Prize! And yet Fleming seems to have had a more “unhistorical spirit” when compared Florey. While biomedical researchers, and their discoveries, are a product of their time, we should not overlook the personal dimension of our historical actors.¹⁸¹ The celebrated physiologist Claude Bernard once wrote, “Art is I, Science is We”,¹⁸² but the personal mark is unavoidable in Science, even if knowledge-making rests on the same method. Science is done by people, and people are different, period.

¹⁸⁰ Brunel 1951 (note 14).

¹⁸¹ Shapin 2008 (note 1).

¹⁸² In Shapin 2008 (note 1), page 6.

I have argued above that picturing modern antibiotics as revolutionary is problematic, namely because it can lead to the neglect of what came before them, namely other antimicrobial drugs with similar virtues. Medical historians have done similar claims in a slightly different context, drawing attention to what they called “a relatively forgotten era of therapeutics in American medicine: the period between the Golden Age of Microbiology and the Antibiotic Revolution”.¹⁸³ I have extended the argument here to draw attention to the fact that we have not only forgotten about the antiserum therapy of that period, as has been convincingly shown,¹⁸⁴ but have also forgotten about virtues and vices of earlier antimicrobial drugs that resemble those of latter ones. In particular, we have forgotten that earlier drugs, such as the arsenical compound Salvarsan and derivatives, drove the emergence of antimicrobial resistance, resembling the modern evolution of antibiotic resistance that is perceived as a major public health concern comparable to climate change nowadays. Antimicrobial resistance was not “absent from clinical medicine” as previously concluded, and indeed fostered reciprocal exchange of knowledge between the clinic and the laboratory, which has been claimed to be distant at the time.¹⁸⁵

Why did we forget about this history? As I mentioned above, societies tend to keep limited records about why they do not think something is worth remembering. I certainly do not claim here that I know the answer to the above question. Narratives revolving around an “antibiotic revolution” most likely had a, if not *the*, pivotal contribution to the apathies about older therapeutics, but it would be naïve to think that a single factor alone can explain such historical amnesia. Arguably, other factors contributed to the forgetfulness about the earlier history of drug

¹⁸³ Podolsky 2006 (note 17), page 147.

¹⁸⁴ Podolsky 2006 (note 17).

¹⁸⁵ Gradmann 2011 (note 6).

resistance, and these include the singularity of disease (syphilis) and its etiologic agent where it emerged, the fact that framing antimicrobial resistance as a relatively recent phenomenon has been having the support of the experts of the field over time, and the lack of practical utility that knowledge about drug resistance had for contemporaries.

Perhaps forgetting about the past is “essential for the process of change in science”, namely biomedical science, following a Kuhnian narrative?¹⁸⁶ I could not disagree more with this claim, and would rather strongly argue otherwise, “History can make science better”.¹⁸⁷ I started this dissertation with a citation from Shaffer to explain why I decided to explore the history of antimicrobial resistance here. I would like to finish by citing Shaffer again, who in the same interview also said, “One of the things that historians of science can offer the social world is a better, more reliable, memory”. I hope this dissertation can contribute towards that goal.

¹⁸⁶ Mendelsohn 2002 (note 147).

¹⁸⁷ Casadevall and Fang 2015 (note 165).

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- Curriculum Vitae -

Educational History:

M.A.	2020	History of Medicine	Johns Hopkins University
		Mentor: Jeremy Greene	
Ph.D.	2015	Systems Biology/Zoology	Oxford University
		Mentor: Kevin Foster	
M.Sc.	2008	Theoretical Ecology	Lisbon University
		Mentor: Frank Hilker	
B.Sc.	2006	Biology	Lisbon University

Other Professional Experience:

Director of Studies in Zoology	2020-	Christ's College/Cambridge
Bye-Fellow in Natural Sciences	2020-	Christ's College/Cambridge
BBSRC Discovery Fellow	2020-	Cambridge University
Wellcome Trust Interdisciplinary Fellow	2019-2020	Cambridge University
Governing Body Fellow	2016-2019	Wolfson College/Cambridge
Herchel Smith Postdoctoral Fellow	2016-2019	Cambridge University

Scholarships, fellowships, or other external funding:

Gen Foundation Award	2020	Gen Foundation
BBSRC Discovery Fellowship	2020	BBSRC
Wellcome Trust Interdisciplinary Fellowship	2019	Wellcome Trust
Herchel Smith Postdoctoral Fellowship	2016	Cambridge University
EPSRC Doctoral Prize	2010	Oxford University
FCT-funded PhD studentship	2010	FCT/Portugal
Prize for top undergraduate students	2004-06	Lisbon University

Key publications, peer-reviewed (articles):

Haas P, **Oliveira NM**, Goldstein RE (2020) Stability and subpopulations in microbial communities. *Phys Rev Research* 2:022036(R).

Niehus R, Picot A, **Oliveira NM**, Mitri S, Foster KR (2017) The evolution of siderophore production as a competitive trait. *Evolution* 71(6):1443-1455.

Oliveira NM, Foster KR, Durham WM (2016) Single-cell twitching chemotaxis in developing biofilms. *Proc Natl Acad Sci USA* 23(113):6532-6537.

Oliveira NM, Martinez-Garcia E, Xavier J, Durham WM, Kolter, R, Kim W, Foster KR (2015) Biofilm formation as a response to ecological competition. *PLoS Biol* 13(7).

Oliveira NM, Niehus R, Foster KR (2014) Evolutionary limits to cooperation in microbial communities. *Proc Natl Acad Sci USA* 111(50):17941-17946.

Oliveira NM, Hilker FM (2010) Modelling disease introduction as biological control of invasive predators to preserve endangered prey. *Bull Math Biol* 72:444-468.

Key publications, peer-reviewed (dissertations/thesis):

Oliveira NM (2015) Evolutionary Competition in Microbial Communities: From Population Dynamics to Single-Cell Behaviour. PhD dissertation. Oxford, United Kingdom.

Oliveira NM (2008) Modelling virus induced control: Regulation of cats and rodents in island ecosystems by FIV. MSc thesis. Lisbon, Portugal.

Oliveira NM (2006) Behavioural fever in the Madeira's wall lizard, *Teira dugesii*: a pharmacological load analysis of potential modulators of thermoregulation. Undergraduate specialization thesis. Lisbon, Portugal.

Publications (in preparation):

Birwa SK, Goldstein RE, **Oliveira NM**. Mechanical stimulation of bacterial bioluminescence.

Fortune G, **Oliveira NM**, Goldstein RE. Biofilm growth under elastic confinement.

Niehus R, **Oliveira NM**, Fletcher AG, Foster KR. The evolution of strategy in bacterial warfare.

Oliveira NM, Wheeler J, Deroy C, Booth S, Durham WM, Foster KR. Bacteria perform suicidal chemotaxis towards antibiotics.