

Circulation of antibiotics: an introduction

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The history of twentieth-century medical drugs is a research subject to which many contributions are currently being made from history of science, medicine and from history of industry¹. The historiography of antibiotics has in good part underlined the role of penicillin as the pioneer miracle since its creation in the 1940s. Penicillin became the emblematic wonder-drug of the post-WWII years and its discovery, production and distribution have been celebrated for half a century as a compelling and relevant historical subject. It also seems to indicate a shift in the history of pharmaceutical industries, in that this history was presumably dominated by Germany until World War II, when the United States took over. The U.S. also stood out among the nations whose use and production of penicillin has been comprehensively studied².

1. Current development in the history of medical drugs is shown in some recent publications. Regarding the history of infections, see Worboys, Michael; Condrau, Flurin, eds. *Tuberculosis, then and now: interdisciplinary perspectives on a post-modern plague*. Montreal: McGill University Press; 2010. Quirke, Vivian; Slinn, Judy, eds. *Perspectives on twentieth-century pharmaceuticals*. Oxford: Peter Lang; 2010. Bonah, Christian; Masutti, Christophe; Rasmussen, Anne; Simon, Jonathan, eds. *Harmonizing drugs: standards in 20th-century pharmaceutical history*. Paris: Gliphe; 2009. Simon, Jonathan; Gradmann, Christoph, eds. *Evaluating and standardizing therapeutic agents, 1890-1950*. New York: Palgrave Macmillan; 2010. Tone, Andrea; Watkins, Elisabeth Siegle, eds. *Medicating modern America: prescription drug in history*. New York: New York University Press; 2007. Bonah, Christian; Rasmussen, Anne, eds. *Histoire et médicament aux 19e et 20e siècles*. Paris: Gliphe; 2005.
2. Hobby, Gladys. *Penicillin. Meeting the challenge*. New Haven-London: Yale University Press; 1985. MacFarlane, Gwyn. *Alexander Fleming, the man and the myth*. London: Chatto and Windus;

The paper in which Fleming described penicillin and its antimicrobial effect was published in 1929 and some exploratory trials followed soon after³. A decade later Howard Florey, Ernst Chain and their colleagues at Oxford University developed a therapeutics agent, although in tiny amounts, which allowed testing on a few promising cases⁴. It was during WWII at the Northern Research Laboratory of the US Department of Agriculture in Peoria (Illinois) where an efficient method of production was devised. This included the addition of corn-steep liquor to the medium and submerged culture growth. With the support of its vice-president Alfred Newton Richards, the Committee of Medical Research of the Office of Scientific Research and Development (OSRD) promoted penicillin production as part of the WWII effort in the U.S. From the pilot plant, the production moved to manufacturing plants through the involvement of pharmaceutical firms such as Merck, Pfizer, Squibb and Lilly. The effectiveness of the treatment of infections with penicillin was confirmed in the treatment of wounds and surgical infections on the war front, including venereal diseases⁵. The rise of this medicine was also closely connected to that of standardised protocols of treatment and evaluation such as the randomised controlled trial (RCT), the first of which was done in 1947 on the antibiotic streptomycin⁶. Collaboration between industry, policy-makers and academic scientists played its part and worked as a pattern for further drugs developments of industrial products from then on⁷.

1984. Bud, Robert. *Penicillin. Triumph and tragedy*. Oxford-New York: Oxford University Press; 2007.

3. Wainwright, Milton; Swan, Harold T. C. G. Paine and the earliest surviving clinical records of penicillin therapy. *Medical History*. 1986; 30: 42-56.
4. Brown, Kevin. *Penicillin man: Alexander Fleming and the antibiotic revolution*. Gloucestershire: Sutton; 2004. On early penicillin trials, Wainwright and Swan, n. 3.
5. Hobby, n. 2, and also the contributions to Parascandola, John, ed. *The history of antibiotics: a symposium*. Madison: American Institute of the History of Pharmacy; 1980. See also Marks, Harry. *The progress of experiment: science and therapeutic reform in the United States, 1900-1990*. Cambridge: Cambridge University Press; 1997; Weatherall, Mark. *In search of a cure. A history of pharmaceutical discovery*. Oxford: Oxford University Press; 1990; Parascandola, John. John Mahoney and the introduction of penicillin to treat syphilis. *Pharmacy in History*. 43; 2001: 3-13.
6. Marks, n. 5; 1997; Podolsky, Scott H. Antibiotics and the social history of the controlled clinical trial. *Journal for the History of Medicine and Allied Sciences*. 2010; 65: 327-367.
7. Swann, John P. *Academic scientists and the pharmaceutical industry: cooperative research in twentieth century America*. Baltimore: Johns Hopkins University Press; 1988. Quirke, Viviane.

The pioneering book by Gladys Hobby has told many important details on the history of penicillin. Later, others emerged to complete the penicillin landscape by connecting it with national policies —histories of success and antibiotic resistance— and by challenging the heroic perception of the discovery⁸. The powerful image of the drug as a hero has been softened however by more recent studies that situate the success and the tragedy, as Bud dramatically put it, of penicillin in a cultural world extremely sensitive to health, wealth and authority⁹.

Many contributions to what could have been perceived as small details exhibit timescapes of practices and distribution of a group of drugs that changed our perception of disease and therapy by creating an image of the likeliness of infections disappearing altogether —brought about by antibiotics and vaccines¹⁰. In parallel to the seemingly miraculous effects of penicillin came the rise of antimicrobial resistances as a clinical phenomenon¹¹. Some microbes were not sensitive to such medicines in the first place, while those that were developed resistant strains, thus leading to the search for new antibiotics, and challenging the hygienic regimes in hospital wards¹².

After the impact of the Second World War on the production of drugs and on the pharmaceutical industry, the post-war period saw a political environment in which infections and the fight against them kept war alive: the war against diseases involved a wide range of actions and agents of

Collaboration in the pharmaceutical industry: changing relationships in Britain and France. Abingdon-New York: Routledge; 2008.

8. Bud, n. 2; Lesch, John E. The first miracle drugs: how the sulfa drugs transformed medicine. Oxford: Oxford University Press; 2007; Greenwood, David. Antimicrobial drugs. Chronicle of a twentieth-century triumph. Oxford: Oxford University Press; 2008, can serve as introductions.
9. Bud, n. 2.
10. On penicillin shortages of its early days, see Adam, David P. «The greatest good to the greatest number». Penicillin rationing on the American home front, 1940-1945. New York-Bern: Peter Lang; 1991.
11. For an introduction see Summers, William C. Microbial drug resistance: a historical perspective. In: Wax, Richard G.; Lewis, Kim; Salyers, Abigail A.; Taber, Harry, eds. Bacterial resistance to antimicrobials. Boca Raton: CRC Press; 2008, p. 1-9; Tansey, E. M.; Reynolds, L. A., eds. Welcome witness seminar. Volume 6. Post-penicillin antibiotics. From acceptance to resistance? London: The Wellcome Trust; 2000. At http://www.ucl.ac.uk/silva/histmed/downloads/c20th_group/wit6.pdf. See also Creager, Angela N. H. Adaptation or selection? Old issues and new stakes on the post-war debates over bacterial drug resistance. *Studies in History and Philosophy of Biological and Biomedical Sciences*. 2007; 38: 159-190; and Gradmann in this issue.
12. Hillier, Kathryn. Babies and bacteria: phage typing, bacteriologists, and the birth of infection control. *Bulletin of the History of Medicine*. 2006; 80: 733-761; and Condrau/Kirk in this issue.

different levels of recognition and responsibilities. In addition, narratives of medicalisation and medication, of health and disease, of health as a right emerged as part of public policies and international strategies that were rising to prominence¹³.

As Quirke and Slinn put it, «geopolitical events, in particular two World Wars, regulatory changes, especially in the U.S. and key developments and discoveries, such as those of diphtheria antiserum, antibiotics and more recently the development of biotechnology have created major discontinuities» in the history of 20th century pharmaceuticals¹⁴. Instead of a revolution produced by a miracle, the history of antibiotics provoked «changes that occurred over a long period, and while there were significant shifts in ideas and practices [...], the balance of continuities and changes was quite uneven across medicine», as Worboys has said on the so-called bacteriological revolution¹⁵. The eventual outcome was also rather an unexpected one. Infectious disease, which many in the after-war years thought would cease to be of relevance, was in fact re-invented instead. The return of such conditions was put in the phrase of the «antibiotic paradox» by Stuart Levy, thereby framing a historical situation in which «antibiotic usage has stimulated evolutionary changes that are unparalleled in biologic history»¹⁶.

The growing authority of the laboratory and of the clinical sciences is among the arguments which should be taken into account when trying to

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13. Quirke, Viviane. War and change in the pharmaceutical industry: a comparative study of Britain and France in the twentieth century. *Enterprises et Histoire*. 2004; 36: 64-83. On the war against diseases see the case of polio in Smith, Jane S. *Patenting the sun: polio and the Salk vaccine*. New York: Anchor Books; 1990; Creager, Angela N. H. *The war against polio*. In: *The life of a virus: tobacco mosaic virus as an experimental model, 1930-1965*. Chicago: University of Chicago Press; 2002, p. 141-184. On primary care as an international agreement promoted by the World Health Organisation, see *Health for all beyond 2000. Declaration of Alma-Ata*. International Conference on Primary Health Care, Alma-Ata, USSR, 6-12 September 1978. At http://www.who.int/hpr/NPH/docs/declaration_almaata.pdf. On the declaration see Navarro, Vicente. A critique of the ideological and political positions of the Willy Brandt report and the WHO Alma Ata declaration. *Social Science and Medicine*. 1984; 18: 467-474.
 14. Quirke, Viviane; Slinn, Judy. Perspective in twentieth-century pharmaceuticals: an introduction. In: Quirke and Slinn, n. 1, p. 1-34 (7).
 15. Worboys, Michael. Was there a bacteriological revolution in late nineteenth-century medicine? *Studies in History and Philosophy of Biological and Biomedical Sciences*. 2007; 38: 20-42; MacFarlane, John T.; Worboys, Michael. The changing management of acute bronchitis in Britain, 1940-1970: the impact of antibiotics. *Medical History*. 2007; 52: 47-72.
 16. Levy, Stuart B. *The antibiotic paradox. How miracle drugs are destroying the miracle*. New York-London: Plenum Press; 1992; Bourdelais, Patrice. *Epidemics laid low: a history of what happened in rich countries*. Baltimore: Johns Hopkins University Press; 2006 (2003).

explain historically the declining impact of infections, the success of antibiotics in their treatment, resistances to their action, and the whole set of institutional changes associated with antibiotics practices. In this regard, the image of Fleming looking through the microscope as a scientific image of the discovery and the discoverer of penicillin is remarkable and remained part of post-war imagery¹⁷.

The central role played by science as expert knowledge in contemporary societies and by its related practices in civil life and governance, kept drugs, and particularly antibiotics, either miraculous or not, at the core of public scrutiny.

More recent studies of penicillin experiences have shown, however, that there was not a standard trajectory of penicillin. Every nation, every factory, every microbial species attacked added to a wide, growing set of histories about penicillin. Even the standard melancholic historical reconstruction of penicillin in Britain, where it was produced as a drug, identified and tested —only to later be mass-produced by the U.S.— has been revised¹⁸. In the Netherlands, as Marlene Burns has shown, during the Nazi occupation an antibiotic named bacinol was clandestinely produced by microbiologist Albert Jan Kluyver at a research laboratory in Delft. In France, trips to the U.S. and back made French production of penicillin possible. In Germany, pharmaceutical companies like Bayer, who had pioneered the sulfa drugs, struggled to catch up with international developments in relation to fungal antibiotics. Meanwhile, U.S. firms were selling penicillin abroad and, later, royalties paid to those firms made production of the drug in other countries possible¹⁹.

17. Chen, Wai. The laboratory as business. Sir Almroth Wright's vaccines programme and the construction of penicillin. In: Cunningham, Andrew; Williams, Perry, eds. *The laboratory revolution in medicine*. Cambridge: Cambridge University Press; 1992, p. 245-292.

18. Liebenau, Jonathan. The British success with penicillin. *Social Studies of Science*. 1987; 17: 69-86.

19. Burns, Marlene. Scientific research in the Second World War. The case for Bacinol, Dutch penicillin. In: Maas, Ad; Hooijmaijers, Hans, eds. *Scientific research in World War II. What scientists did in the war?* London-NewYork: Routledge; 2009, p. 44-61; Bartmann, Wilhelm. *Zwischen Tradition und Fortschritt. Aus der Geschichte der Pharmabereiche von Bayer, Hoechst und Schering von 1935-1975*. Stuttgart: Steiner; 2003; Shama, Gilbert; Reinartz, Jonathan. Allied intelligence reports on wartime German penicillin research and production. *Historical Studies on the Physical and Biological Sciences*. 2002; 32: 347-367. On France, see Gaudillière, Jean-Paul. *Inventer la biomedicine: la France, l'Amerique et la production des savoirs du vivant*. Paris: La Découverte; 2002, chapter 1; Gaudilliere, Jean-Paul; Gausemeier, Bern. *Moulding*

And, of course, there are historiographies of many other anti-infective agents waiting to be explored. This dossier aims at contributing to fill some of the gaps in the history of antibiotics.

Circulation

All these national histories from the post-war period remind us that despite the internationalism of the drug market and its underlying science, drugs continued to be handled within national frameworks. While standardisation and internationalisation were part and parcel of the evaluation and production of antibiotics, the view on the circulation of such medicine serves to highlight the national policies involved in the post-WWII era. These policies shaped early production of penicillin in the laboratory, at the bench of modest research settings as well as in the factory²⁰.

National politics and policies notwithstanding, penicillin as an object was transnational through travelling. News of its therapeutic capabilities against infections travelled first—in publications and mouth to mouth. The drug itself, in its ampoules in boxes, travelled along with protocols of its use. The doses and types of infections that could be successfully treated also circulated, as did methods of industrial manufacturing.

As a piece of technology bred in laboratories, antibiotics were one of the most important ingredients for the new gods of welfare, peoples' and nations' wealth and health—and for the technological optimism of the age that found one of its personifications in pills designed to control disease and enhance life²¹. A recently published history of sulfa-drugs shows a complex landscape of practices from chemistry laboratories to the factory, from dyes to therapy, transitions which suggest the circulation of knowledge and practices that featured contemporary cultures²².

The idea of circulation is introduced here to elaborate on the travels involved in knowledge production. As knowledge whose practices have

national research systems: the introduction of penicillin to Germany and France. *Osiris*. 2005; 20: 180-202. On Spain, see Santesmases, María Jesús. Delivering penicillin: the clinic, the hero and industrial production in Spain, 1943-1952. In: Quirke, Vivian; Slinn, Judy, eds. *Perspectives on twentieth-century pharmaceuticals*. Oxford: Peter Lang; 2010, p. 91-117.

20. Gaudillière, 2002, n. 19, chapter 1.

21. Bud, n. 2, p. 97-115.

22. Lesch, n. 8.

been, and still are, in search of reproduction and verification, the permanent adjustment of laboratory and factory practices of drugs production was linked to travels to and from different geographical places and professional domains, and to bodies and times of antibiotics²³.

Some of these trajectories were physical ones: batches of antibiotics travelled, protocols and instructions of use and production were distributed and received in particular local settings, promoted by national authorities. By suggesting the concept of circulation, we would like to draw attention to the issue of standards themselves embarking on such journeys. The papers included in this dossier explore the trajectories of antibiotics standards regarding its production, microbiological practices, clinical standards, patents as regulators, and research practices. As a set, the dossier contributes to the study of how activities involved in producing and using antibiotics influenced each other and eventually shaped public health and epidemiology²⁴.

Bacterial resistances to antibiotics contributed to shaping research and medical practices. In that way, the phenomenon contributed to an increasing knowledge about the mechanisms of antibiotics action at the cellular level, and also provided the basis upon which further search for new antibiotics developed. Penicillin was the first of a long series of antibiotic drugs: streptomycin's successful effect in the treatment of tuberculosis followed, as did chloramphenicol and tetracyclines. Figures of treatment results, of cure and resistances, travelled as well, and public health and epidemiology became part of the issue²⁵.

Embedded in every ampoule, flask, coated-pill, were the practices of producing, distributing and using the substance. Antibiotics linked practices in different social and cultural domains, and within them standards moved around from chemistry laboratories to fermentation pilot plants. Clinicians, researchers, patients and health authorities as well as fiction and non-fiction recollections would shape antibiotics cultures²⁶.

23. Gaudillière, Jean-Paul; Hess, Volker, eds. *Ways of regulating: therapeutic agents between plants, shops and consulting rooms*. Berlin: Max Planck Institut für Wissenschaftsgeschichte; 2009.

24. Macfarlane; Worboys, n. 15

25. Weatherall, n. 3.

26. Regarding non-fiction, see the history of Hitler taking penicillin during WWII. Wainwright, M. *Hitler's penicillin. Perspectives in Biology and Medicine*. 2004; 47: 189-198. On fiction, the best known may be Carol Reed's, *The third man* (1949), based on the novel of the same title by Graham Green. A Spanish film was also produced on the same issue: *Mercado prohibido* (1952), by Xavier Setó.

The image of the U.S. Army delivering penicillin after the war is a powerful one, just as there are many others regarding success, failures, public opinion, local settings, moral economies, marketing and labelling, brand policies. Antibiotics' power and images did not come to be spread from a single source. Some of the individuals and collectives who became agents in antibiotics history are part of this dossier.

American penicillin manufacturing success was part of the dramatic development of biomedical sciences in that country, of the intense history of research practices and policy-making that established global scientific and industrial leadership during the Cold War years. Regulation of the prescription of new drugs was part of the history, connected to the emergence of welfare state policies in some European countries and to insurance policies in the U.S.²⁷. Agents, however, acted locally. Beyond trends toward globalisation and toward any apparent homogenisation through standardisation, nations remain relevant for historical narratives regarding the history of antibiotics.

The contributions to this dossier

From an earlier collaborative project on drug trajectories made by historians of medicine and science, a European network program, DRUGS, was approved by the European Science Foundation in 2007 with the aim of developing a history of drugs standards in the 20th century. Such standards were understood as dynamic structures that are a typical feature of the history of the 20th century²⁸.

This dossier includes a selection of papers presented at the workshop «Circulation of Antibiotics: Journeys of drugs standards», held in Madrid in June 2008 as part of ESF DRUGS Networking Program²⁹. Each contribution provides its particular narrative that links the history of antibiotics with national politics, with that of infections and resistances of such infections. These articles also situate in places and times the microbiological practi-

27. Tone; Watkins, n. 1. Daemmrich, Arthur. *Pharmacopolitics: drug regulation in the United States and Germany*. Chapel Hill-London: University of Carolina Press; 2004.

28. Bonah, Christian; Gaudillière; Jean-Paul; Gradmann, Christoph; Hess, Volker. Standard drugs and drug standards. A comparative historical study of pharmaceuticals in the 20th century. In: Bonah; Masutti; Rasmussen; Simon, eds., n. 1 p. 17-27.

29. The set of papers presented at the workshop was uploaded at http://drughistory.eu/downloads/Madrid_Preprint.pdf

ces which were at the origins of industrial manufacturing of penicillin by fermentation.

Resistance is reviewed by Christoph Gradmann as a concept that would remain central from Paul Ehrlich's works and colonial medical practices for tropical infections up to the present. Since, however, resistance as a concern for clinical medicine only became relevant during the Second World War, its history followed other trajectories after Ehrlich's observation of the phenomenon in 1907. As Gradmann shows, induced resistance was employed as a laboratory tool in cell biology, experimental pharmacology and genetics long before it came to be of interest in clinical medicine. Offering evidence for the existence of so-called chemoreceptors, it was firmly connected to Ehrlich's side chain theory of immunity.

The roots of penicillin production are revisited by Robert Bud in his contribution about chemistry and fermentation chemists who invented the practices that led to culturing and isolating the drug. Fermentation and microbiology remained instrumental in antibiotics manufacturing and laboratory research³⁰. Fermentation was the kind of process —biological and chemical— that formed the practices of antibiotics production. Two circumstances, that the works of Bud's craftsmen had mainly commercial purposes and one of the leading chemists was a member of the Nazi party, explain the apparent invisibility of fermentation skills in the industrial construction of penicillin. From chemistry and microbiology to biotechnology, this trajectory may well be the pattern of development of antibiotics production, a combination of knowledge and practices of two disciplines that joined efforts in twentieth-century drugs development. In this process disciplines, their practices and cultures, did matter.

Penicillin was indeed a cultural and political agent of its time. Knowledge about this drug and the medical and industrial practices associated with it shaped the post-WWII era, involving research, diplomatic and political agendas with the aim of producing penicillin to cure infections. This is the case of Italy told by Mauro Capocci. One of the first experts in the drug, Ernst Chain, moved from Oxford to Rome to promote a project for manufacturing penicillin funded by the Italian state. The integration of Italy in the international environment of post-WWII Allied politics while promoting national industry —practices that evoke the Spanish policies of the Franco

30. Bud, n. 2.

dictatorship after WWII, in particular regarding penicillin— featured the introduction of penicillin manufacturing in Italy, where many actors played a part in the penicillin research network with the aim of making Rome one of the nodes of such a network³¹.

Patents not only protected invention rights but also provided details of the technical methods for penicillin manufacturing, thus acting as a guarantee of productivity and reproducibility as well as mediators between different professional domains. As the contribution by Ana Romero shows, the history of antibiotics intersected with the history of patenting and industrial regulation. The documents studied in Romero's article show the journeys of penicillin, the paths taken in those travels, and how the new drug spread worldwide after the Second World War, and particularly in Spain, precisely by circulating the methods for its industrial manufacturing.

Hospital infections are presented as an agent in the history of clinical practices and chemotherapy in Britain by Flurin Condrau and Robert Kirk. Hospital infections and antibiotic-resistant bacteria were redefined by the interplays of differing interests of bacteriologists and clinicians. Antibiotics were part of an «arsenal» for medical success, while the clinic witnessed and reacted to a context of ever-adapting hospital infections during the emergence of the National Health Service's claims to provide effective healthcare to the population. Condrau and Kirk situate antibiotic resistances in the middle of the promising origins of the welfare state, where health care was one of the articulators of policy-making in Britain.

The production of antibiotics involved the factory and the laboratory. When a screening program was set up in Madrid in 1954, as a collaboration of Merck and CEPA (a Spanish firm that was manufacturing penicillin in Spain), the resulting research program was organised like industrial manufacturing. Santesmasés shows how both the factory system of production —a production line of craftsmanship to obtain new anti-infectious substances from soil samples— and Selman Waksman's program of research on new antibiotics, which successfully led to isolating streptomycin, interacted and interchanged practices. Microbiological material and methods were agents of both research and industrial manufacturing, thus reinforcing the strong connections in practices as well as conceptually between industrial manufacturing and research practices. Antibiotics thus became a set of

31. Santesmasés, n. 19.

substances which contributed to research not only in the treatment of infections and the drug industry, but in microbiological research as well.

History of antibiotic standards shows co-production of standards and markets, of products and production processes, of therapeutic specificity, of protocols. At the same time, such standards have been local products in particular moments of twentieth-century history. And often such standards remain national or sectorial, significant for a professional domain. This suggests that permanent feedback took place between agents and professional spaces involved in the history of antibiotics. Not only drugs circulated but a diversity of standards did so as well, and contributed to the rearrangement of antibiotic cultures and practices.

Early knowledge and practices played their role as a sort of original reference, as a guide to manage the new product, to prescribe it and to manufacture it, to search for new ones. It needs to be emphasised that a question remains open, namely to what extent this early reference —penicillin at the end of WWII— carried standards in itself or if it became the sample from which standards were developed. As knowledge about successful therapies arrived before the industrially-produced penicillin itself, references and standards contributed to homogenisation, which means possibilities to replicate, to reproduce results and production. By circulating, by moving around and crossing national and professional boundaries, antibiotics, its effects and its standards were permanently reconstructed. ■

