

Innovators, deep fermentation and antibiotics: promoting applied science before and after the Second World War

Robert Bud (*)

(*) Science Museum, London. Robert.bud@sciencemuseum.org.uk

Dynamis

[0211-9536] 2011; 31 (2): 323-341

Fecha de recepción: 1 de abril de 2010

Fecha de aceptación: 3 de febrero de 2011

SUMMARY: 1.—Introduction. 2.—Know-how and deep-fermentation. 3.—Wartime. 4.—Post-war. 5.—Conclusion: on the disappearance of stories.

ABSTRACT: The historiography of penicillin has tended to overlook the importance of developing and disseminating know-how in fermentation technology. A focus on this directs attention to work before the war of a network in the US and Europe concerned with the production of organic acids, particularly gluconic and citric acids. At the heart of this network was the German-Czech Konrad Bernhauer. Other members of the network were a group of chemists at the US Department of Agriculture who first recognized the production possibilities of penicillin. The Pfizer Corporation, which had recruited a leading Department of Agriculture scientist at the end of the First World War, was also an important centre of development as well as of production. However, in wartime Bernhauer was an active member of the SS and his work was not commemorated after his death in 1975. After the war new processes of fermentation were disseminated by penicillin pioneers such as Jackson Foster and Ernst Chain. Because of its commercial context his work was not well known. The conclusion of this paper is that the commercial context, on the one hand, and the Nazi associations of Bernhauer, on the other, have submerged the significance of know-how development in the history of penicillin.

KEY WORDS: Penicillin, organic acids, Konrad Bernhauer, know-how, applied science.

PALABRAS CLAVE: Penicilina, ácidos orgánicos, Konrad Bernhauer, saber-hacer, ciencia aplicada.

1. Introduction

It is perhaps regrettable that antibiotics are more often seen historically as medicines which were triumphally invented by a few scientists, than as technologies exemplifying complex processes of innovation across the world. Penicillin proved important to engineers, industry and to governments as

well as to scientists, doctors, and patients. Its history was also far more interesting than wartime and post-war publicists would recall.

While the triumph of the American production programme is well known, the memory of a vigorous prewar network of pioneers of deep fermentation dedicated to the manufacture of organic acids seems to have been overlooked. The early historiography expressed the wish to celebrate American technology and British science. This had the effect of obliterating the memory of the role of Konrad Bernhauer, the key German scientist affiliated early and strongly with the Nazi Party who, in wartime, was responsible for the death of at least one Jewish colleague as well as for his earlier important developments in biochemical engineering¹. Perhaps not surprisingly, no effort seems to have been made either by himself or by his friends to remind the public of his once-important role and recovering the lost importance of those developments may still be a morally ambiguous enterprise. However locating the pre-history of the production of organic acids through fermentation helps us understand the specific background of an iconic development, and more generally the process of developing «know-how» in «applied science».

The globalisation of penicillin during the incipient Cold War, in the years immediately after the Second World War, was fast, visible and interesting, and made the medicine a political as well as medical resource. This led not just to the replication of American methods and products across the world, it was characterised too by the development of novel derivatives and a rapidly developing manufacturing process that made possible new medicines. It was expressed in new journals and brought together diverse techniques and innovations under the title «biotechnology»². I return to this topic after studying both biotechnology and penicillin in the belief that historians' interest in complex global interactions could contribute to the

1. It is perhaps indicative that the otherwise excellent American Chemical Society treatment of «deep tank fermentation», in its penicillin history brochure by Judah Ginsburg which is available on the web http://portal.acs.org/portal/acs/corg/content?_nfpb=true&_pageLabel=PP_ARTICLEMAIN&node_id=882&content_id=WPCP_010013&use_sec=true&sec_url_var=region1&__uuid=ac6caf16-a23a-4326-8fa5-17f091d87219, mentions no work on deep fermentation other than that of Pfizer.

2. For work on biotechnology, see Bud, Robert. *The uses of life: a history of biotechnology*. Cambridge: Cambridge University Press; 1994.

wider discussion of the process of innovation in science and technology which even now is poorly understood³.

As is well known, the Oxford group in England managed to produce small quantities and to demonstrate antibacterial efficacy. British industry had neither the will nor the competence to scale up their work quickly⁴. Consequently, in July 1941, Howard Florey and Norman Heatley flew to the United States and over the subsequent three years US industry developed deep fermentation methods that made penicillin available for all military casualties who required it and soon after accessible to civilians too. The critical development was the perfection of a method of deep fermentation of the aerobic mould cells without contaminating the brew or disrupting the cells. So with penicillin came the perfection and developing uses of the stirred tank fermenter, a rarely acknowledged pillar of the modern age. The provision of cheap and ample penicillin to support allied troops at D-day, within three years of the drug's arrival in the United States, was a huge achievement. In the cases of both technology and product, this was however, to quote Churchill, the end of the beginning not the beginning of the end.

In subsequent developments, penicillin, which was still then injected into patients eight times a day, would be chemically reconstructed. Its absorption would be slowed so it would last in high concentrations within the blood for eight hours rather than three, it would be made sufficiently stable to be taken by mouth, and later still to stand up to the challenge of aggressive bacteria exuding the destructive enzyme penicillinase. The technology of manufacture would be applied to other medicines, many of them antibiotics, but also to others, such as the steroids, chemically and therapeutically quite different. The centres of production would move: first to Britain, then to Austria, the Netherlands and Japan and later to China.

Of course historians are familiar with accounts of the dissemination of both science and technology. The transfer of science is described typically

-
3. Fagerburg, Jan. Innovation: a guide to the literature. In: Fagerburg, Jan; Mowery, David C.; Nelson, Richard R., eds. *The Oxford handbook of innovation*. Oxford: Oxford University Press; 2005, p. 1-26; the classic work is Rosenberg, Nathan; Landau, Nathan, eds. *The positive strategy. Harnessing technology for economic growth*. Washington DC: National Academies Press; 1986. See also Howells, Jeremy. *Tacit knowledge, innovation and technology transfer. Technology analysis and strategic management*. 1996; 8: 91-106; however, see Athreya, Suma; Godley, Andrew. *Internationalization and technological leapfrogging in the pharmaceutical industry. Industrial and corporate change*. 2009; 18: 295-323.
 4. Bud, Robert. *Penicillin: triumph and tragedy*. Oxford: Oxford University Press; 2007.

in terms of PhD families. The model disseminator of science is still Justus von Liebig and his model of «chemist breeding» remains the archetypical model of how to disseminate the methods of a school⁵. Beyond the tuition provided by the doctoral supervisor, the academic publication, typically the scholarly article is the method by which science and its methods spread across the globe. Co-citation clusters indicate relationships between scientific traditions and ongoing research projects, and we know that methods are the best cited of all types of papers.

The dissemination of «know-how» in manufacturing is less easy to track. A generation ago Derek de Solla Price suggested that patents are to technology what those scholarly papers are to science⁶. However, in neither science nor industrial practice are such simplistic descriptions of the mechanism of dissemination sufficient. Above all in the promotion of applied science we have few models for the mechanisms by which methods, skills, experience and contacts are shared, coalesce and spread.

In the story of penicillin itself there were very few patents —an issue which proved hard to understand in the postwar world. In common with most other countries, before the Second World War Britain had not permitted the patenting of drugs and by the time penicillin had reached the United States it was not patentable there either. Many of the processes of manufacture were developed at the federal Peoria research laboratory whose discoveries were, by law, public domain within the United States. Attempts to patent overseas by Andrew Moyer, a Peoria researcher, were contested by the Merck corporation which did not enforce rights in Britain. It is true that during the 1950s the British paid significant sums to US pharmaceutical companies. Thus the Glaxo company paid significant funds to the Merck corporation. In the decade to 1956 this amounted to half a million pounds equivalent to about 3% of the company's net profits⁷. Yet these payments were not to cover the cost of royalties. In response to public disquiet in Britain there had been a thorough investigation within Merck to confirm that the British were paying no royalty payments to the United

5. Morrell, J. B. The chemist breeders: the research schools of Liebig and Thomas Thomson. *Ambix*. 1972; 19: 1.

6. De Solla Price, Derek J. Is technology historically independent of science? A study in statistical historiography. *Technology and Culture*. 1965; 6 (4): 553-568.

7. Bud, n. 4, p. 72.

States. Instead they were paying for unpatented «know-how» relating to manufacture using deep fermentation.

2. Know-how and deep-fermentation

The history of penicillin development therefore meanders between the history of science and that of technology. Between them is an ill-defined area that has long been called «applied science». Many scientists, perhaps most in the last century, have located their own work in this zone. Yet it is very weakly served by historians⁸. With few exceptions, the generic nature of the product has not been generally reflected upon. However, Peter Galison in his studies of the diverse tribes of physicists has shown how different communities can exchange «know how». His concern is the exchange between scientists concerned with «basic» knowledge, however others have shown how it can be applied to applied science⁹.

The development of such know-how had gone back far beyond the Second World War. The technology of submerged fermentation had first been developed at the small New York firm of Pfizer during and immediately after the First World War. It grew out of an interest in producing the preservative and flavouring-agent citric acid. Traditionally produced from lemons, in 1893 the German Carl Wehmer had shown that it could be produced too by *penicillia*. Wehmer's choice of organism however required careful control of conditions to prevent the production of oxalic acid too. So it was a considerable advance when, in 1917, the American-government dairy-chemist James Currie made his discovery that it could be made

-
8. Johnson, Ann. What if we wrote the history of science from the perspective of applied science? Historical Studies in the Natural Sciences. 2008; 38 (4): 610–620. Though see Kline, Ronald. «Construing technology» as «applied science»: public rhetoric of scientists and engineers in the United States, 1880-1945. Isis. 1995; 86: 194-221. See also Bud, Robert; Gummett, Philip. Don't you know there is a war on? [Introduction]. In: Bud, Robert; Gummett, Philip, eds. Cold War hot science. Amsterdam: Harwood; 1997. My own continuing research is exploring this area.
 9. Galison, Peter. Image and logic: a material culture of microphysics. Chicago: University of Chicago Press; 1997. Also see Gorman, Michael E. Levels of expertise and trading zones: a framework for multidisciplinary collaboration. Social Studies of Science. 2002; 32 (5/6): 933-938; Gorman, Michael E.; Groves, James F.; Shrager, Jeff. Societal dimensions of nanotechnology as a trading zone: results from a pilot project. In: Baird, David; Nordmann, Alfred; Schummer, Joachim, eds. Discovering the nanoscale. Amsterdam: IOS Press; 2004, p. 63-73.

prolifically by the mould *Aspergillus Niger* fed with a solution of sucrose. Because the mould was aerobic, it needed to grow in vessels with good exposure to air. Having moved to the small Brooklyn firm of Pfizer, Currie experimented with deep tanks but could not get them to work effectively and instead developed a process based on long shallow trays.

The value of citric acid was considerable. Over 5,000 tons was produced in the United States alone in 1929, with a reported value of four and a half million dollars¹⁰. In 1927 this process became strategically essential to the US, Britain and France when Italy cut off the export of calcium citrate¹¹. Immediately US exports grew, though from 1935 they fell again as the British developed their own capability through the work of such companies as Kemball Bishop.

During the 1920s work on citric acid production proceeded in a number of centres, but above all in the German University in Prague. There the chemist Konrad Bernhauer had shifted his attention from inorganic chemistry to the chemistry of industrial fermentation processes. He published preponderantly in *Biochemische Zeitschrift* edited by Carl Neuberg, director of the Kaiser Wilhelm Institute for Biochemistry and Experimental Therapy. This was an academically prestigious context, at the same time his interests were very practical. By 1930, one finds his work cited in a Czech patent which dealt with the production of citric acid through deep fermentation¹².

Moreover, during the 1920s interest moved to the production of other acids, particularly gluconic acid which was a useful industrial cleaner. This could be produced using the same *Aspergillus Niger* that Currie had shown could produce citric acid.

In 1929 the Pfizer Corporation started submerged fermentation of gluconic acid, but still using small flasks. A 1931 patent application suggests a typical size of one litre¹³. Strikingly, the paper describes the critical characteristics of powerful stirrer and vigorous aeration. It is likely that

-
10. Lockwood, Lewis B.; Moyer, Andrew J. The production of chemicals by filamentous fungi. *Botanical Review*. 1938; 4 (3): 140-164.
 11. Wells, Percy A.; Herrick, Horace T. Citric acid industry. *Industrial & Engineering Chemistry*. 1938; 30 (3): 255-262.
 12. Kanhäuser, Franz. Process for the production of citric acid. US patent 1,779,001 granted 2 October 1930. Filed in Czechoslovakia, 16 December 1927. This patent cites production in an environment of «artificial convection of agitated nutrient solutions».
 13. Currie, James W.; Kane, Jasper; Finlay, Alexander. Process for producing gluconic acid by fungi. US patent number, 1,893,819 filed 9 February 1931.

productivity was not yet high: a German paper of the time suggests just 19% conversion of sugar in a fermentation lasting 40 days compared with 90% when using a shallow layer¹⁴. Nonetheless, this was the technique that would be used so triumphally a decade later in the manufacture of penicillin.

Pfizer was certainly pioneering but it was far from alone. In Prague, Bernhauer published a process for producing gluconic acid by fermentation in 1927. With his advice, in 1936 the major chemical company of Boehringer began to manufacture the acid¹⁵. Interest also continued within the US government's Department of Agriculture from whence Currie had originally come. Two young chemists who had recently graduated from George Washington University and moved to the capital's «Color and farm waste division» of the Bureau of Chemistry and Soils, Horace T. Herrick and Orville E. May, were brought in to work with the established microbiologist Charles Thom (a former collaborator with Currie) and his colleague the mycologist Margaret Church in studying gluconic acid production by penicillium moulds¹⁶. Their paper cited the preeminent stimulus of Konrad Bernhauer, the German-Czech chemist.

A year later the two brash young men, Herrick and May, were evangelizing at the Institute of Chemistry of the American Chemical Society on the theme «microbiological chemistry is the chemistry of the future»¹⁷. The paper of these two young recruits to the profession concluded, «Of course there is money eventually in it, but remember this —the dollar rolls more willingly down the road constructed and made smooth by the hands of scientists». Their «sermon» was published the following year in

-
14. Amelung, H. Wachstum und Säurebildung von *Aspergillus niger* unter Wasser. *Chemische Zeitung*. 1930; 54: 118.
 15. On Boehringer see Marschall, Luitgard. *Im Schatten der chemischen Synthese: Industrielle Biotechnologie in Deutschland (1900-1970)*. Frankfurt am Main: Campus; 2000.
 16. May, Orville. E.; Herrick, Horace. T.; Thom, Charles; Church, Margaret B. The production of gluconic acid by the *Penicillium luteum-purpurogenum* group. *Journal of Biological Chemistry*. 1927; 75: 417-422. The team is treated to some extent by Neushul, Peter. «Science, government, and the mass production of penicillin». *Journal of the History of Medicine and Allied Sciences*. 1993; 48 (4): 371-95. This draws upon the memories of Percy Wells who joined the team in the 1930s, it however does not accurately represent the work or careers of Herrick, May, Thom and Church in the 1920s. This can be deduced by tracing back publications and their own educational trajectories. It seems that only the mycologists received an obituary in a major journal. On Margaret Church see Hesseltine, C. W. Margaret B. Church, 1889-1976. *Mycologia*, 1990; 82 (1): 144-147. See also Raper, Kenneth B. Charles Thom 1872-1956, *Mycologia*, 1957; 49: 134-150.
 17. Herrick, Horace T.; May, Orville. Molds and chemical manufacture. *Industrial and Engineering Chemistry*. 1929; 21: 618-621.

Industrial and Engineering Chemistry under the title «Molds and Chemical Manufacture». They reported on the potential for manufacturing a wide number of organic acids and reported on the work of their own laboratory in replacing sucrose by corn sugar (a cheap product of distressed Midwestern agriculture) as a fermentation substrate. While the 41 references in their paper did include a paper by Currie and one other American, there was no sense that either Pfizer in particular or the US in general was in the lead in this technology. Quite to the contrary, their paper was dominated by German references (including Bernhauer) and indeed also three papers by the Japanese scientist Takahashi (including two collaborations with the future leader of the Japanese fermentation community Sakaguchi)¹⁸.

Over the next few years Herrick and May developed their research programme. In March 1933 they addressed the American Chemical Society again, but this time the annual meeting itself and together with two younger colleagues, A. J. Moyer and P. A. Wells. Again their paper was published in *Industrial and Engineering Chemistry*¹⁹. They reported how the numerous published accounts of production of organic acids by deep fermentation had stimulated their own work²⁰. They used a series of bottles into which air was

-
18. It is worth emphasizing that in 1929/1930, two Japanese scientists carefully documented the history of use of *Aspergillus Niger* from the 18th century to the present. Tamiya, H. and Morita, S. Bibliographie von *Aspergillus* von 1729 bis 1928. Botanical Magazine (Tokyo), 1929; 43: 60-71, 145-156, 179-189, 237-249, 281-291, 321-332, 371-381, 427-438, 501-515, 577-589, 625-633. 44; 1930: 1-7, 79-89, 139-150, 209-218, 251-261, 305-316, 375-386, 421-431.
 19. May, Orville E.; Herrick, Horace T.; Moyer, Andrew J.; Wells, Percy A. Gluconic acid. Production by submerged mold growths under increased air pressure. *Industrial and Engineering Chemistry*. 1934; 26: 575-578.
 20. May, Moyer and Wells, n. 19 did cite the work of Currie but they explained their main stimulus as the work of Germans; «Consideration of the work of Schreyer and of Thies pointed to the possibility of establishing the production of gluconic acid by submerged mold growths on a practical basis». For Schreyer see, Schreyer, Reinhold. Säuerungs versuche mit dem Pilz *Aspergillus Fumaricus*. *Biochemische Zeitschrift*. 1928. 202: 131-156; and for Wilhelm Thies see Untersuchungen über den Einfluss der Bedingungen auf die Säurebildung des Schimmelpilzes *Aspergillus fumaricus*. *Zentralblatt für Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene*. 1930; 82 (2): 321-347. This seems to have been the result of a doctoral thesis Both Schreyer and Thies, and indeed another oft-cited author Johannes Amelung (PhD 1926) were associated with the Bacteriological-chemical laboratory in the Technische Hochschule in Hannover. Schreyer in turn cited predominantly two authors, his countryman Bernhauer and the Russian mycologist, W. S. Butkewitsch who was also widely cited. In 1922 Butkewitsch published the first article in which gluconic acid was the main product of a fermentation. The two distinguished British scientists (former assistants of Chaim Weizmann) A. C. Thaysen and L. D. Galloway, in their textbook, *The microbiology of starch and sugars*. Oxford: Oxford University Press; 1930, 96 recognised as the first report of gluconic acid being produced by fungi, Molliard Morin.

introduced under pressure and constant pressure. Just as the publication of this team, and its sequels through the 1930s, cited the work of the Germans, so the patents of Bernhauer and of Currie were interconnected. A Bernhauer patent was, for instance, licensed by Pfizer in 1932²¹. In 1936 the German Boehringer company launched its own gluconic acid fermentation facility.

The early 1930s had seen a veritable explosion of work in the area by the scientists in the leading laboratories. The first volume of *Annual Reviews in Biochemistry* contained an article by Nicholas Iwanow, of Leningrad's Institute of Plant Industry, which quantified the growth of interest in the biochemistry of *Aspergillus*. Between 1927 and 1930 he decried an increase in the number of works published annually, roughly doubling from 129 works to over 300²².

A key new partner in this international trade in ideas emerged in 1932. Jan Kluyver had taken over the key microbiology chair at the technical university in Delft in the Netherlands. In 1932 he published the first theoretical paper to explore the process of deep fermentation²³. His apparatus was tiny but his contribution much revered, so that for instance Bernhauer would cite it as the seminal work in his 1936 textbook on fermentation processes. Within a few years Kluyver's favourite student Van Niel brought his school to the United States when he obtained a position in California at the marine laboratory of Stanford University²⁴. The Americans also continued

Sur une nouvelle fermentation acide produit par le *Sterigmatocystis nigra*. Comptes Rendus Academie de Science Paris. 1922; 174: 881-882. They suggested however that among the mass of later work, Bernhauer's three articles were the most important. See Bernhauer, Konrad. Zum Problem der Saurebildung durch *Aspergillus niger*. Biochemische Zeitschrift. 1924; 153: 517-521; Bernhauer, Konrad. Über die Säurebildung durch *Aspergillus niger*. II. Mitteilung - Die Bildung von Gluconsäure. Biochemische Zeitschrift. 1926; 172: 313-323; Bernhauer, Konrad. Beiträge zur Enzymchemie der durch *Aspergillus Niger* bewirkten Säurebildungsvorgänge. Zeitschrift physiologische Chemie. 1928; 177: 86-106.

21. US patent 1,849, 53, «Production of gluconic acid», Application filed 26 November 1927, assigned to Charles Pfizer.
22. Iwanoff, Nicolaus N. The biochemistry of the fungi. *Annual Review of Biochemistry*. 1932; 1: 675-697.
23. Perquin, L. H. C.; Kluyver, Jan. Zur Methodik der Schimmelstoffwechseluntersuchung. *Biochemisches Zeitung*. 1933; 266: 68 and Über die Bedingungen der Kojisaurebildung durch *Aspergillus flavus*. *Biochemisches Zeitung*. 1933; 266: 82. On the context of this work see Woods, Donald D. Albert Jan Kluyver. 1888-1956. *Biographical memoirs of Fellows of the Royal Society*. 1957; 3: 109-128.
24. On the relationship between Van Niel and Kluyver see, La Rivière, Jan Willem Maurits. The Delft School of Microbiology in historical perspective. *Antonie van Leeuwenhoek*. 1997; 71: 3-13.

to study on the continent of Europe. When the Wisconsin microbiologist Myron Johnson wished to increase his expertise in 1932, he spent time in Bernhauer's laboratory²⁵.

Lest this image of an international network of laboratories be too idealized, one must recall how marginal the individuals and research projects were to most of science and to national communities. In the 1930s the universities and laboratories concerned were marginal and low status. It is perhaps indicative that the central German programme was not even within Germany itself. In the US too the centres were far from such centres as Harvard and MIT. When in 1932 a rare American review article of the literature on citric acid fermentation came out, it was a product of the low status New Jersey land grant college, the Rutgers Agricultural school and the author acknowledged the inspiration of a then scarcely known teacher S. A. Waksman²⁶. A soil microbiologist, he was immured in a status gully between agriculture and medicine, the normal home of microbiologists²⁷. On the other hand he had an eye to industrial opportunities. As another Waksman student, Boyd Woodruff, would later recall, stimulated by the work of Kluyver and the success of Pfizer, Waksman was interested in developing a citric acid process to aid Pfizer's competitor, the Merck Corporation, to which he was a consultant²⁸.

3. Wartime

This albeit low status but industrially well-connected network was progressively smashed from the late 1930s. Following the Munich agreement and the British and French abandonment of Czechoslovakia in the autumn of 1938, the Germans took over Prague during March 1939. The ancient Charles University and the national technical university were closed, and their

See also Spath S. B. Cornelius B. van Niel and the culture of microbiology, 1920-1965. Ph D Thesis, University of California, Berkeley, 1999.

25. On Marvin Johnson's visit to Prague see, Interview with Robert H. Burris, University of Wisconsin-Madison Archives. Oral History Project, Madison, 1983.
26. Porges, Nandor. Citric acid production by *Aspergillus niger*. American Journal of Botany. 1932; 19 (7): 559-567.
27. Waksman S. A. My life with the microbes. London: Hale; 1958.
28. Boyd Woodruff interviewed 17 October 1997, ASM Centennial Archival Project, American Society of Microbiology Archives, University of Maryland.

faculties moved to the German University, which now became the central institution. Many of the staff were fired and were therefore unemployed and subject to forced labour, if not murdered. On the other hand, Bernhauer seems to have been a Sudeten German nationalist and was himself an energetic member of the Nazi party. This was no move of convenience. On 23 March almost immediately the Germans entered Prague, he joined the SS²⁹. He became the secretary of the party-run association of lecturers in Bohemia. He was a prime mover in the takeover of the Charles University by the German University. Wartime records would show that he denounced colleagues and helped the party find and subsequently murder those with Jewish associations. In September 1941 he was rewarded for his work with a recommendation for promotion to the senior rank of *Sturmbannführer*³⁰. He prospered academically too. In February 1941 he had been promoted to full professor³¹. He was also rewarded for his faithfulness by Goering who ran the four-year plan with an institute on enzymology responsible alcohol and acetic acid³².

The Germans of course conquered the Netherlands too. Wishing to give the image of respect to their «aryan» brothers, many gentile activities were allowed to continue and Kluyver's laboratory remained open. Until the US entered the war, Kluyver was able to keep in touch with Van Niel in distant California.

-
29. Beurteilung. Betr: SS-Bewerber Professor Dr Konrad Bernhauer, Prag. 20 June 1939. Bundesarchiv, 6400/0029/11 SSO, Bernhauer Konrad.
 30. Heydrich to Reichsführer-Personalhauptamt, 13 September 1941. Bundesarchiv, 6400/0029/11 SSO, Bernhauer Konrad.
 31. Announcement made by the Führer, 22 February, Bundesarchiv, 6400/0029/11 SSO, Bernhauer Konrad.
 32. For Bernhauer's position see Miškova Alena; Svobodny, Petr. Hermann Hubert Knaus (1892-1970) Mediziner. Die Jahre 1938–1945 an der Medizinischen Fakultät der Deutschen Universität in Prag. In: Gettler, Monika; Miškova, Alena, eds. *Prager Professoren 1938-1948*. Essen: Klartext; 2001, p. 429-441. For the account of the denunciation of his colleague, see Miškova, Alena. *Die Deutsche Universität Prag im Vergleich mit anderen Deutschen Universitäten in der Kriegszeit*. In: Lemburg, Hans, ed. *Universitäten in nationaler Konkurrenz. Veröffentlichungen des Collegium Carolinum*, Volume 86. Oldenbourg; Oldenbourg Wissenschaftsverlag: 2003, p. 167-193 (180-181). See also Simon, Gerd, ed. *Wissenschaftspolitik im Nationalsozialismus und die Universität Prag Dokumente eingeleitet und herausgegeben von Gerd Simon*. Tübingen: Gesellschaft für interdisziplinäre Forschung. At http://tobias-lib.uni-tuebingen.de/dbt/volltexte/2001/217/pdf/gif002_komplett.pdf for Bernhauer's work to subsume the Charles University.

With war coming to the United States, even the Washington group was thrown into disarray. The Arlington property occupied by the Color laboratory was required for a vast new military complex that would be dubbed «The Pentagon». Herrick, May and their younger colleague Andrew Moyer were uprooted to a new laboratory that was to be established a thousand miles to the northwest of Washington near the small Midwestern town of Peoria under the title of Northern Regional Research Laboratory, which opened after much disruption in mid-1941. However they still came under the Department of Agriculture and kept in close touch with their mentor and protector, the great microbiologist Charles Thom.

Such was the context into which penicillin was injected in 1941. The Oxford team who had isolated penicillin first hoped that they could obtain significant quantities of the drug from British industry. Indeed the first company to manufacture for them was Kemball Bishop, a licensee for Pfizer's citric acid process, which adapted their tray technology to growing penicillium mould. However, the company was small and had no experience at all in deep fermentation. So Florey turned to American industry.

Florey's good American connections took him immediately to the heart of the fermentation network. When he arrived in the United States with Norman Heatley on 4 July 1941, he went straight to his old Yale friend John Fulton who then took him to meet Charles Thom, the distinguished USDA microbiologist. In turn, Thom sent the visiting Englishmen to his chemist protégés who, though exiled in Peoria, now once again had a laboratory. Drawing on a decade of experience with both deep fermentation and penicillium moulds, Moyer immediately showed how penicillin could be plentifully produced. He also found a more productive strain of mould than the English had brought.

That other centre which through Currie had been closely connected with USDA, the Pfizer company, now deployed Moyer's findings and their own long experience with deep fermentation. Led by Jasper Kane, who had begun his career as assistant to Currie in the company's earliest deep fermentation work two decades earlier, the team built a 7,000 gallon fermenter in the autumn of 1943 and upscaled yet again early the following year. Meanwhile, the Merck Corporation hired Jackson Foster, a former student of Waksman who had gone on to work with Van Niel in California before returning to the East Coast, to help exploit the English observations.

Interestingly, even in wartime, all connection with Bernhauer's experience was not severed by the Americans. The German's bible of fermentation

was translated into English in 1942, and although in typescript, at least three copies of this translation would survive to the present day³³. In Prague, Bernhauer, learning of the work at Oxford, developed his own deep fermentation process and would later chair the German national committee charged with producing the drug. However, in the home of organic chemistry and the sulphonamide drugs, the effort was accorded little priority until the very end of the war, by which time it was too late. Prague was bombed, and Bernhauer discussed fantastical dreams of building a plant in the more peaceful environment of the Austrian Tyrol with his Austrian assistants Richard Brunner and Karl Schroeder who had worked in a brewery there. Unofficial, but nonetheless sophisticated and successful, efforts to produce penicillin had also been carried out underground in Prague and in the industrial town of Olmütz. In Delft too, the home of Kluyver and his students, work continued on penicillin without German sanction³⁴.

4. Post-war

So the war ended with Pfizer triumphant, its investment in fermentation technology over quarter of a century vindicated. Bernhauer's team, by contrast, was broken up. They dashed south to the Austrian border but only Brunner, an Austrian national, was allowed to cross. Bernhauer made his way to Germany where he would work in industry during the 1950s³⁵. He then regained an academic position at the University of Stuttgart where during the 1960s he opened an institute of biotechnology and trained a generation which led German biotechnology in the 1970s and early 1980s³⁶. However,

-
33. Amerine, Maynard A.; Wheeler, Louise B. A check list of books and pamphlets on grapes and wine and other related subjects 1938-1948. University of California Press; 1951 cites «Practical chemistry of fermentation, by Dr. Konrad Bernhauer ... 27 illustrations. Translated by Bernard Freyd. [Washington DC: Works Projects Administration C1942?] ... Loose leaf; reproduced from typewritten copy». The World catalog cites copies at the National Agricultural Library in Beltsville, UC Davis and University of Washington, Seattle.
 34. Burns, Maelene; Van Dijck, Piet W. The development of the penicillin production process in Delft, The Netherlands, during World War II under Nazi occupation. *Advances in Applied Microbiology*. 2002; 51: 185-200.
 35. Koenig, Joseph. *Die Penicillin-V Story. Eine Erfindung aus Tirol als Segen für die Welt*. Innsbruck, Haymon Verlag; 1984.
 36. This was emphasized to me personally by Hanswerner Dellweg who became director of Berlin's Institut für Biotechnologie and learned about biotechnology in the 1950s when

Bernhauer's wartime crimes were overlooked rather than forgiven. When he died in 1976, this distinguished pioneer of two generations of biotechnology, and active Nazi, was accorded only one short obituary (dealing just with his scientific contributions, in the newsletter of the Vienna brewing research institute written by Richard Brunner)³⁷.

Brunner himself however successfully established a penicillin factory in the Austrian Tyrol and was joined by Karl Schroeder on his release from post-war imprisonment. That plant, under the title of Biochemie AG, would develop the first effective oral penicillin and before it ceased to make penicillin at the beginning of the 21st century it would be the world's largest producer, outstripping its American contemporaries. Bernhauer would have been pleased. The Delft plant prospered too in the post-war years. Even today the Delft Institute of technology continues to be a centre of expertise.

The immediate post-war years also saw a distinctively new kind of disseminating the expertise in penicillin production that had moved so quickly from the outer periphery of science to its centre. The drug and the new technology became a means for nations to express international standing. The Canadian foreign minister Lester Pearson saw an opportunity to express his country's independent standing and offered to give away the design of the deep fermentation penicillin plant built in Toronto through the United Nations Relief and Reconstruction Agency (UNRRA). The design and expertise would come from Canada though the individual pieces of equipment would be supplied by American companies.

Initially five countries were chosen to benefit from this offer: Italy, Czechoslovakia, Poland, Ukraine and Belarus (the latter two were at the time nominally independent members of the USSR). The acceptance by Italy

he worked with Bernhauer. See also. A man at the cradle of bioprocess engineering. *Bioprocess Eng.* 1986; 1 (1): 2-2. An example of an important pupil was Fritz Wagner who became director of the important department of biotechnology of the GBF who took his doctorate at Stuttgart under Bernhauer. See Schügerl K. Makers of bioprocess engineering. *Bioprocess Engineering.* 1994; 11 (4): 121-121. It was not only in Germany that Bernhauer was respected. In 1960 he was invited to the editorial board of the newly founded journal *Biotechnology and Bioengineering*, the first modern journal with the word biotechnology in its title.

37. Brunner, Richard. In Memoriam. Konrad Bernhauer. *Mitteilungen der Versuchsstation für das Gärungsgewerbe in Wien.* 1976; 2: 22. Despite an early expression of interest to the present author, Bernhauer is hardly mentioned in the post-war history of Stuttgart University, Becker, Norbert; Quarthal, Franz, eds. *Die Universität Stuttgart nach 1945. Geschichte, Entwicklungen, Persönlichkeiten.* Stuttgart: Jan Thorbecke; 2004.

came about through the energetic work of Domenico Marotta, director of the *Istituto di Sanità Superiore* who in 1948 recruited the Oxford penicillin Nobel-Prize-winner Ernst Chain to lead his penicillin enterprise³⁸. Chain prevailed upon Marotta to get the offer of a by-now obsolete commercial plant converted into a pilot plant for the development of penicillin science and technology. With a hundred scientists and engineers, Chain built a new sort of centre. This was far larger than its prewar ancestors, such as the teams of Bernhauer and Herrick. Launched in 1951 with a major international conference, it came to contain 30 x 10 litre fermenters, 9 x 90 litre fermenters, 3 x 300 litre fermenters and 1 x 3,000 litre fermenter. It employed 20 chemists and biochemists, 3 physical chemists, 9 microbiologists, 2 chemical and 2 mechanical engineers, 2 glass blowers, 15 mechanics, 4 electronics technicians and 40 general technicians, and a large number of visiting scientists. There were two groups: biochemistry and chemical microbiology³⁹.

Chain's laboratory is best known as the incubator for the Beecham research project that culminated in the development of the semisynthetic penicillins at the end of the 1950s. This particularly successful international commercial collaboration was, however, far from unique for the institute. The Chain papers tell a story of widespread international consultations with such companies as Astra in Sweden and Bayer in Germany, Hindustan antibiotics and the Weizmann Institute in Israel⁴⁰. Chain consulted not just in his own right, sharing personal expertise, but also on behalf of the Institute as a whole which conducted investigations on behalf of clients. They dealt with such issues as foaming, penicillin derivatives, fermenter design and training of staff.

The papers of Chain in the archive at the Wellcome Institute are a rich document of his life on the move and in correspondence, particularly with his chief client, the Swedish Astra company. Interestingly, he would write to the Germans in English, though when offered a prize in Germany

38. See Capocci, this volume.

39. For the launch conference see International Congress for Microbiology, 6 vols. Roma, 1953. The scale of Chain's enterprise is described by him in *My Activities at the Istituto superiore di sanita*, C13 box 12, Chain Papers, Wellcome Library for the History and Social Study of Medicine.

40. For Chain's work in India see Tyabji, Nasir. Gaining technical know-how in an unequal world: Penicillin manufacture in Nehru's India. *Technology and Culture*. 2004; 45: 331-49.

he spoke in German. Clearly the line between Chain's role as the leader of the Rome team and his personal life were constantly being renegotiated.

In 1961 Chain accepted a professorship at Imperial College London but only relinquished his Rome position three years later⁴¹. Even then he ensured an exact replica of his Rome pilot plant was built in South Kensington by the Italian team, including the chemical engineer Gualandi. His work as a trader went on. Among the clients of his new centre would be the Ranks for which he carried out important work on the project which yielded the mycelial protein meat substitute, Quorn⁴².

Chain's institute itself embodied Galison's trading zone through which ideas, expertise and skills could travel through the activities of entrepreneurial traders. Its engineers and scientists communicated not just by publications and patents. Through the contracts brought in by their entrepreneurial leader, «tacit knowledge» and judgements honed in one context could be applied in another.

A somewhat similar role was played by Jackson Foster, at first on behalf of the Merck Corporation but later as a professor at the University of Texas before his untimely death in 1966⁴³. Having played a distinguished role in Merck's wartime penicillin developments, he was loaned to General McArthur to help the Japanese on behalf of the United States Government. Foster taught the Japanese using internal Merck documents, but often rather than specifying details he facilitated the exploitation of Japan's long standing expertise in microbiology to the advantage of a new era of pharmaceutical manufacture. He prompted his hosts to recognise the equality of scientists and engineers and to move away from a traditionally science-headed hierarchy. He would be remembered for his wise sayings such as, «How successful you are depends on your exploitation of these 3 watchwords: organization, cooperation, and action». In emphasizing the importance of automated safety devices he emphasized, «Civilization has learned not to trust human nature». Foster would be both successful and revered.

41. The best biographical treatment is Abraham E. Ernst Boris Chain. 19 June 1906-12 August 1979. *Biographical Memoirs of Fellows of the Royal Society*. 1983; 29: 43-91.

42. I am grateful to the archivist of Imperial College for making available the records of the biology departments at the College.

43. On Jackson Foster see Wyss, Orville. Obituary: Jackson W. Foster. *ASM News*. 1966; 32 (2): 1966. For his work in Japan after the Second World War, see Bud, n. 4, p. 94-95.

Foster's trading activities would not just be one way. At the end of the 1950s he toured the world's leading microbiological laboratories on behalf of the US military. With his distinguished reputation he had unique access, and was able for instance to visit and report upon the Institute of Microbiology in Soviet-bloc Prague⁴⁴.

The work of Chain and Jackson Foster was not, of course, unprecedented in science. From early in the 20th century the A. D. Little company had been consulting to the chemical industry and developing the category of chemical engineering. Going back further, the role of consultant chemist even preceded the role of academic researcher in Britain and elsewhere⁴⁵. However the role of such consultants has perhaps been neglected in our understanding of innovation in the twentieth century. Certainly its commercial context has meant it has had a low profile within science, and company clients have not highlighted its importance either.

5. Conclusion: on the disappearance of stories

This paper has shown that in the two decades preceding the Second World War, Americans and Europeans, particularly Germans, were trading know-how in deep fermentation. Patents, doctoral and post-doctoral study and consultancy were all means of gleaning other people's knowledge in exchange for funds and status —within the community if not without. The wartime development of penicillin was made possible by the rich body of know-how this had developed. Again, the rapid post-war diffusion of penicillin manufacture and the development of new techniques were made possible by this persistent pattern. Men such as Chain and Foster came and went in the trading zones of bioprocess chemistry. Even Bernhauer returned to this prewar cultural space he had occupied so successfully.

These practices and the people have been overlooked. Perhaps it might have been otherwise. During the 1960s there was an attempt, supported by Bernhauer, to define the category of biotechnology in terms of fermentation technologies. In 1974 a key report, produced by the German Chemical

44. Foster, Jackson. A microbiologist looks at Czechoslovakia. Office of Naval Research, London Office, 9 October 1962; Technical Report ONRL-74-62.

45. On the role of the consultant, see Bud, Robert; Roberts, Gerrylynn. Science versus practice. Chemistry in Victorian Britain. Manchester: Manchester University Press; 1984.

Industry Association, entitled «Biotechnologie» hardly mentioned molecular biology and instead focused on the potential of fermentation. One could perhaps speculate whether if that endeavour had been successful, the obliteration of the prewar networks and their research would have been reversed⁴⁶.

However, the wartime and postwar story had been formalized without reference to prewar German work. The history of penicillin is typically recounted in terms of science at Oxford and the technology of building fermenters by the Americans. As early as 1945 Vannevar Bush began his classic report *Science the Endless Frontier* with an affirmation of the penicillin story:

«We all know how much the new drug, penicillin, has meant to our grievously wounded men on the grim battlefields of this war —the countless lives it has saved— the incalculable suffering which its use has prevented. Science and the great practical genius of this nation has made this achievement possible»⁴⁷.

Bush then went on to argue that now that Europe which had been the source of science could no longer be relied upon, America would have to fill the gap. He would propose funding through the elite universities. In constructing this argument, the laborious work of the pre-war fermentation chemists, biochemists and engineers was overlooked. The memory of Bernhauer was erased and with it the network of which he was so important a part.

Four decades ago, Derek de Solla Price reflected on the ways in which narratives are constructed in the wake of great successes. Certainly penicillin was one of those. We may reflect too on the narratives which are not told and on the functions of not telling those stories.

46. See Bud, n. 2. I am grateful to Professor Hanswerner Dellweg for talking to me about Bernhauer's attitude to the word «biotechnology».

47. Bush, Vannevar. *Science: the endless frontier: a report to the President*. Washington D. C.: United States Government Printing Office; 1945.

Acknowledgements

I am grateful to the Science Museum, London, which has funded this research. I am grateful to the participants at the conference ESF Networking program DRUGS conference and to participants at the «Innovation Economy and History of Science and Technology: The Making of the Contemporary Pharmaceutical Research System», Barcelona, May 2009, particularly Lou Galambos, for their penetrating comments. I am grateful too for the Bernhauer papers, researched and provided by Das Bundesarchiv, Germany. For the opportunity to discuss the contribution of Konrad Bernhauer, I am grateful to Hanswerner Dellweg, and I am grateful to the late Boyd Woodruff for his memories of Jackson Foster. ■

