Pilzkrieg: the German wartime quest for penicillin

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Citation: SHAMA, G., 2003. Pilzkrieg: the German wartime quest for penicillin. Microbiology Today, 30 (August), pp. 120 - 123.

Additional Information:

- This article was published in the journal, Microbiology Today [© SGM]. The website is at: http://www.sgm.ac.uk/

Metadata Record: https://dspace.lboro.ac.uk/2134/11049

Version: Accepted for publication

Publisher: © Society for General Microbiology (SGM)

Please cite the published version.
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Pilzkrieg: The German Wartime Quest for Penicillin.

Gilbert Shama

The last 15 years or so have seen the appearance of a number of articles and biographies that have attempted to dispel many of the myths surrounding the discovery of penicillin and its development as a useful antibiotic. The story of this remarkable compound is invariably presented as a triumph of Anglo-American collaboration at a time of need. However, attempts to produce penicillin during the Second World War were not confined to Britain and the USA. Parallel efforts were also taking place in Germany. It is, however, only in the last 10 years that historians have turned their attention to this particular twist in the story of penicillin. The fact that their story is not more widely known about is because the events have only been recounted by German historians writing in their own language. Yet, paradoxically, the first accounts of German attempts to manufacture penicillin were written in English in intelligence reports which were compiled immediately after the defeat of Germany in May 1945. The reports were prepared under the auspices if the British Intelligence Objectives Subcommittee (BIOS) and the Combined Intelligence Objectives Subcommittee (CIOS). They were originally given security classifications, but those reports dealing with purely industrial or commercial information were rapidly declassified and were published by the HMSO from 1946 until well into the 1950s. This account draws both on the BIOS and CIOS reports as well as on more recent German studies in order to present a portrait of the research carried out and its principal participants.

The Shadow of Germany

Towards the end of 1939 Howard Florey and Ernst Chain at the Sir William Dunn School of Pathology at Oxford secured a grant to study antibacterial substances. They chanced to start with penicillin and by the summer of 1940 had succeeded in isolating it and in showing that it possessed powerful antibacterial action in vivo. They published their work in the medical journal The Lancet. Also in that summer, Florey and a few trusted colleagues succumbed to a fear of imminent German invasion that was sweeping the nation and transferred spores of Penicillium notatum onto the
linings of their jackets: should the invasion occur, at least one of them might succeed in escaping to the USA with the precious mould.

A threat of a more concrete kind reached Florey in April 1941. German scientists, he learned, were keen to examine penicillin and would attempt to acquire some through the Swiss pharmaceutical company Ciba Geigy. Florey acted swiftly and wrote to Alexander Fleming as well as R. St. John Brook, the head of National Collection of Type Cultures, warning of the consequences of *P. notatum* falling into German hands. He also wrote to Sir Edward Mellanby, chairman of the Medical Research Council which had partly been funding the work on penicillin. In his reply, Mellanby assured him that he was ‘miles ahead’ of any competition and that there was no point in suppressing publication on penicillin in the national interest because effective antibacterials - information on the sulphonamides - were so widely available. Florey took the hint and in August 1941 a second paper, this time containing a wealth of technical information, appeared in *The Lancet*. Included were details of the growth medium for culturing *P. notatum*, a method of assaying penicillin and illustrations of the spouted ceramic culture vessels used to grow the mould as well as the apparatus for harvesting the penicillin-containing broth. Most importantly, the article revealed the procedure for extracting penicillin from crude fermentation broths. It was this crucial step that had defeated not only Fleming, but later also Harold Raistrick at the London School of Hygiene and Tropical Medicine and Roger Reid in the USA. In short, the paper provided all the information required to set up a penicillin manufacturing process – assuming, that is, that one possessed Fleming’s strain of *P. notatum*.

*Research and development of penicillin*

Evidence from a number of sources indicates that both of *The Lancet* papers reached Germany, via neutral Sweden. Its initial distribution on arrival in Germany was not determined purely on technical grounds. There was a pecking order with those having high Nazi Party connections being at the top of the list. One who had early access to it was Theodore Morell, Hitler’s personal physician. Morell was not highly regarded in German medical circles and after the war Albert Speer described him as a ‘screwball interested only in money’. The involvement of such disreputable individuals probably added to the delays in the *Lancet* articles reaching those who
could make proper use of them. The consensus of opinion is that penicillin research began in Germany sometime in late 1942. Therefore the *Lancet* papers would probably have had to reach *bona fide* scientists in the late summer of 1942 – fully two years after the appearance of the first paper.

News of penicillin spread quickly throughout the German pharmaceutical community. Companies of all sizes as well as universities and research institutes became involved in a scramble to produce the antibiotic. Prominent among the former were most of the divisions of IG Farbenindustrie – Hoechst, Elberfeld, Marburg, and also E. Merck of Darmstadt, Schering AG of Berlin, Schott and Genossen of Jena and Knöll of Ludwigshafen.

The first stumbling block facing these would-be producers was that of obtaining a penicillin-producing strain of *Penicillium*. On receipt of his warning about the undesirability of Germany acquiring penicillin, Fleming assured Florey that, whilst he had sent out many samples of his culture of *P. notatum* all over the world, none as far as he could remember had gone to Germany. His memory was at fault; a certain Dr Schmidt at the IG Marburg Works had received a culture from Fleming some years before the war. Schmidt had never attempted to do anything with the strain but with a revival of interest in penicillin, he attempted to grow it. He failed, and perhaps doubting his mycological technique, he then sent the culture to Schering in Berlin but they too were unsuccessful. This was not the last word on this celebrated strain as far as Germany was concerned. There were at least two further attempts to acquire it. There were suspicions in Germany that both the Pasteur Institute and the University of Copenhagen possessed Fleming’s mould. In fact Fleming had personally given Andre Lwoff of the Pasteur Institute a culture. However it is doubtful if a culture existed in Copenhagen but Professor K. A. Jensen had heard about penicillin and had succeeded in isolating his own strains. In any event, the Germans did not succeed in obtaining Fleming’s strain.

With the fall of Holland, Germany had at its disposal, what Florey described in a letter as ‘the best (mould) culture collection in the world.’ This was the Centraal Bureau voor Schimmelcultures (CBS) located at Baarn, near Utrecht. German microbiologists were not slow to arrive at this realisation. Fleming had never
deposited his culture with the CBS but their culture catalogue showed that they held a closely related strain, *Penicillium notatum* (Westling). The archives at Baarn contain scores of requests for this from the companies listed above as well as from other smaller firms and universities in Germany. The strain had been deposited at Baarn many years before and would have been sub-cultured many times without regard to its antibiotic productivity – indeed in total ignorance that it even possessed such a trait. It was at best only a poor penicillin producer. There is no evidence that it ever featured prominently in German penicillin research. Interestingly, a paper published in *Nature* in November 1942 characterised the strain as a producer of notatin.

It was not long before German microbiologists set about isolating their own strains. Some microbiologists worked independently whilst others appear to have shared their strains with colleagues from other laboratories. Notable among the latter was Andreas Lembke. Lembke was the Director of a Research Institute in Kiel that was concerned primarily with milk technology. Lembke had mycological experience and had assembled at Kiel a fairly extensive collection of moulds. The entire collection was destroyed in bombing late towards the end of the war. In 1943, together with Joseph Von Kennel and Joseph Kimmig, he wrote what is possibly the only article on antibiotics published in Germany during the War. This work described the isolation of moulds belonging to a number of genera including *Penicillium*, *Aspergillus*, *Fusarium* and *Cephalosporium*, all of which allegedly produced anti-bacterial substances. Lembke and his co-workers named these substances ‘mykoins.’ Kimmig, who had previously worked on novel sulphonamides, came to devote much effort to penicillin research and was supported in this by Schering AG. Hans Knöll, a microbiologist employed by the glass company Schott and Genossen, also provided strains to many other researchers. Elsewhere, at IG Elberfeld, Maria Brommelhues, working in Gerhard Domagk’s (the pioneer of sulphonamides) laboratory had isolated some 50 strains of penicillia. She was aware that not all of the antibiotics produced by these strains were penicillin and she was able to separate the penicillin producers in her collection from those that produced other secondary metabolites such as notatin, and patulin.

The practices and procedures described in the second of Florey’s *Lancet* papers seem to have been widely adopted by most workers in Germany. In particular, penicillin
was being assayed by variants of the bioassay originally developed in Oxford by Norman Heatley. After 1942 publication of process details in Britain and the United States on penicillin production were subject to fairly strict controls. However, these controls were not total and useful information did occasionally get out into the public domain. More than one group of workers in Germany seem to have been aware that corn steep liquor (CSL) had a beneficial effect on penicillin yields. Whether they knew quite what it was is a different matter; one contemporary reference mistranslates it as 'maisalkohol.' Most researchers in Germany employed surface culture techniques for growing their strains. A variety of vessels were used but Hans Killian at the University of Breslau employed rectangular vessels identical to those used in Oxford, but made of glass rather than ceramic. However, it emerges that a significant number of research workers had experimented with submerged culture. Not surprisingly they reached the same conclusions as those arrived at by American microbiologists at the Northern Regional Research Laboratories in Peoria, Illinois. This was that strains isolated on their ability to produce penicillin in surface culture are not necessarily able to produce similar yields in submerged culture. How German scientists came to know of the potential advantages of submerged culture is not certain. Reports that this method was being used for large scale production did appear in American chemical industry trade journals in 1944 and news of this may well have reached Germany. It is certain that many details of the American programme were known about as an article published in Chemiker Zeitung, a chemical trade journal makes clear. The article published in October 1944 revealed details of the existence of the War Production Board (WPB) and quotes the names of American companies involved in penicillin production as well as their production targets. It is also possible that Konrad Bernhauer of the University of Prague was promoting submerged fermentation. Bernhauer had written a standard work on fermentation chemistry in which the principles of submerged fermentation were laid out.

Whilst most of the technology employed in Germany for penicillin research and development was based on Anglo-American developments, German workers did conduct at least some original research. Not all of it was guaranteed to result in improved penicillin yields. When workers at the IG Hoechst works encountered persistent contamination, they countered with the use of ‘antibodies’ such as ether and chloroform. More interestingly, some German microbiologists tried using mixtures of
strains in order to increase penicillin yields. Others attempted to grow penicillia on waste liquors from paper mills. One entrepreneur named Bruno Bottcher had developed an electro-osmotic diaphragm technique for purifying penicillin. Schering AG were sufficiently impressed to supply Bottcher with penicillin which was conveyed to him from Berlin in vacuum flasks. Joseph Kimmig had even attempted to understand how penicillin acted and although he arrived at an erroneous conclusion—that it disrupted the succinic acid cycle in bacteria—his work reveals a serious commitment to penicillin research. Heinz Oeppinger at IG Hoechst interviewed immediately after the war by Harold Raistrick, apparently impressed Raistrick with his design for a ‘rotating drum device’ for submerged fermentation.

Organic chemists in Germany must have asked themselves, just as their counterparts in Britain and the USA did, whether they might not be able to synthesise penicillin chemically. The only information available to the former was a formula for penicillin published in Nature by Heilbron and his co-workers in 1942. Heilbron’s formula was subsequently shown to be incorrect. However this intelligence, and further developments which did lead to the correct formula and eventual synthesis by a combined Anglo-American team, were subject to a very strict publication embargo. Highly purified material is an absolute requirement for meaningful formula and structural studies and this was never available in Germany during the war.

One intelligence report accounts how scientists at IG Marburg claimed to have ‘practically pure penicillin’. The writers of the report describe being shown ‘a small piece of moist looking orange coloured, clumpy material’—their incredulity is almost tangible. Research workers at a small number other laboratories claimed to have supplied some or all of their penicillin to chemists for ‘structural studies’. Hopes of elucidating the structure of penicillin and then synthesising it chemically probably explain the involvement of the distinguished chemist Richard Kuhn. Kuhn had been nominated for the Nobel Prize in 1938 for his work on the structure of vitamins and carotenoids, but forbidden by a decree of Hitler’s from accepting it. Kuhn had been working on synthetic antibacterials, and claimed that one of his compounds ‘3065’ (ethanedione, bis(5-bromo-2-hydroxyphenyl) was allegedly ‘300 times’ more potent than penicillin. What is interesting is his source of penicillin. The German War Ministry had in its possession some Allied penicillin which had been captured by the German army. Other than the fact that it was manufactured by Burroughs Wellcome,
nothing is known of where it was taken or of its date of capture. One can only speculate as to the delay which this penicillin incurred in reaching the various German laboratories and the conditions to which it had been subjected to whilst in transit. It seems likely that by the time it reached Kuhn it had lost most of its activity. Kuhn was correct in that 3065 does indeed possess antibacterial power, but his conclusions about its efficacy compared to penicillin were certainly wrong. As Head of the Kaiser Wilhelm Institute in Heidelberg, Kuhn was in an influential position and his findings must have fuelled German suspicions that the power of penicillin had been exaggerated by the Allies for propaganda reasons.

Heatley’s assay technique, widely used in Germany, would have detected any antibiotic substance that inhibited the growth of the ‘target bacterium’, *Staphylococcus aureus*. With penicillia being isolated from a variety of sources by several groups of workers, it seems possible that some researchers in Germany may not have been working with penicillin but with other secondary metabolites. Some in Germany understood this. The Canadian microbiologist Roger Y. Stanier was charged with preparing a report for BIOS on applied microbiological research in Germany and met and interviewed a number of German scientists. Andreas Lembke told him that at least one of the mykoins he had isolated - mykoin C - was chemically distinct from penicillin. Lembke cited the fact that mykoin C’s spectrum of antibacterial activity was distinct from that of penicillin. As evidence, he told Stanier that it was not inactivated by penicillinase. Kuhn had not been the only scientist to receive captured Allied penicillin, and it is quite possible that Lembke was able to reach his conclusions because he had access to some ‘authentic’, but low potency, penicillin. Stanier’s curt assessment was that mykoin C was probably ‘a mixture of clavacin with some penicillin.’

Some penicillin was certainly produced in Germany, although it was never produced on a sufficiently large scale as to be of anything remotely approaching strategic value. Theodore Morell’s diaries show that penicillin was used by him to treat Adolf Hitler’s injured hand following the July 1944 bomb plot. The penicillin may have been produced at Olomutz in Czechoslovakia. The facility at Olomutz had been seized from its original Jewish owners and placed under Theodore Morell’s control. Morell’s actual contribution to penicillin work was insignificant but he employed two
scientists, Kurt Mulli and Wolfgang Laves to supervise work at the plant. Both of these men had Jewish ancestry. Morell went on to receive the Iron Cross in 1943 for the discovery of ‘bacteriostatic substances from the lower fungi.’ Information about this came to the attention of the press in Britain and The People ran a story headed ‘Huns steal new drug.’ References to clinical trials occurs a number of times in the BIOS and CIOS reports. Learning from Lembke that some of the antibiotics he had produced were sent to a hospital in Segebeck for clinical trials, Stanier took himself there. He was unimpressed with what he found and although the clinicians at Segebeck provided accounts of the penicillin’s efficacy in treated dermatological conditions, Stanier concluded that no meaningful clinical trials had been carried out.

Hoechst claimed to have manufactured a number of penicillin containing products including, ‘penicillin wound powder’ and penicillin impregnated bandages, neither of which, they hastened to add, were ever supplied to the German armed forces. In some cases researchers appear unwilling to submit their material for such trials believing it to be too impure.

*The Ultimate Failure of German Efforts*

Why did the German programme not succeed in producing useful quantities of penicillin? There are a number of reasons. Immediately after the war the technical intelligence teams touring Germany attributed this failure to an over-reliance on the sulphonamides. Although these were important products for the German pharmaceutical industry, this conclusion appears too simplistic now. Penicillin research was taking place in Domagk’s own laboratory under Maria Brommelhues and even Joseph Kimmig, who owed his reputation to the sulphonamides, became a convert to penicillin.

As the first antibiotic, penicillin was to herald a new era for pharmaceutical companies. Here was a compound which seemed to defy the best efforts of organic chemists, a group of professionals that had served the German pharmaceutical well. Success in producing penicillin demanded application of established technology – fermentation - to the production of an entirely novel compound. In the United States the experience of the fermentation industry was rapidly and efficiently mobilised by the WPB to the services of penicillin production. The main industrial participants in
German penicillin work were the constituent companies of IG Farben, Schering and Merck. These had all achieved notable success with synthesised compounds and would have found the necessary transition difficult to make. In fact considerable fermentation experience existed in Germany. Germany had been at the forefront of fermentation technology from a time dating to before the First World War when a substantial proportion of their fodder requirements were met by yeast grown specifically for the purpose. In the inter-war years the fodder yeast industry had declined, but in 1939 it again assumed a strategic significance. Some companies conducted their operations in fermentation vessels of 600 m$^3$ capacity. The failure to bring together existing fermentation experience and the considerable fermentation capacity in Germany proved costly.

Whilst it is clear that useful collaborations between different research workers and companies were established, it is also evident that there was also wasteful duplication and with a race to produce penicillin, duplication of effort would have been damaging. The absence of a central reference laboratory was a definite disadvantage. Microbiologists may have been freely exchanging strains but there seems not to have been any systematic attempts to identify the most productive ones. Whilst Heatley’s assay was in general use, there appeared to have been no attempts to standardise the technique throughout Germany. At the IG Elberfeld Works, the scientists told their Allied interrogators that they were producing penicillin of a potency of 40 Oxford units. However, on further questioning they were forced to admit that the potency was in reality 40 ‘Elberfeld Units’. When in July 1941, penicillin process development was in effect transferred to the NRRL, Florey took Heatley with him specifically so that he could instruct the microbiologists at Peoria on the finer points of his assay.

The scale of the American programme to produce penicillin was estimated to have cost about $14 million. Unfortunately no comparable data exists for the uncoordinated German effort. But it was certainly very considerably less. As instance, one recent article refers to Richard Kuhn as having received 25,000 Reichs Marks for ‘research on antibacterial compounds’; this was equivalent to approximately $10,000.
Both the British and the American wartime programmes owed their success to central co-ordination. German realisation of the need to co-ordinate the disparate activities came too late. Heinz Oeppinger was present at a meeting held under the Chairmanship of Professor Paul Rostock in which Konrad Bernhauer was put in charge of a co-ordinating committee. Oeppinger said that ‘by the time of that meeting, we could get no yeast, no acids, no supplies or materials. It was all over.’

Further Reading


Dr Gilbert Shama is a Lecturer in the Department of Chemical Engineering, University of Loughborough, Loughborough, LEICS., LE11 3TU.

Tel. 01509 222514; Fax 01509 223923:

Email g.shama@Lboro.ac.uk