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Zones of Inhibition? The Transfer of Information Relating to Penicillin in Europe during World War II

Gilbert Shama

Department of Chemical Engineering, Loughborough University, Loughborough, Leics.,
LE11 3TU, UK

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Abstract

Alexander Fleming published his first description of penicillin in 1929, but the journal articles that were to propel penicillin from its relative obscurity were those of Howard Florey and his co-workers at Oxford University. These were published in *The Lancet* in the early years of World War II and although wartime conditions restricted the flow of information on penicillin throughout Europe, they never succeeded in shutting it off altogether. In Germany an information-gathering initiative was established in the early phases of the war to systematically copy and distribute British and American scientific articles. A similar, though less well resourced, operation was permitted to function in Occupied France. Both of these operations were to yield up information on penicillin to their respective scientists. However, workers in other countries of occupied Europe fared less well; there was a dearth of information on penicillin in Holland but despite this, activity to produce the antibiotic still took place. Central to the production of penicillin at this time was access to a strain of Fleming's strain of *Penicillium notatum*, and an attempt to explain how this particular strain found its way to various European laboratories is given here.

Keywords: Penicillin, Information transfer, World War II, *Penicillium notatum*

I. Introduction

Full appreciation of the therapeutic potential of penicillin really only came to be made in the early years of the Second World War, and in many ways the war was to shape penicillin's development. On the one hand there was unprecedented cooperation amongst British and American pharmaceutical companies. Whilst on the other, steps were taken to prevent the means for producing penicillin from falling into enemy hands. News about penicillin inevitably leaked into the public domain through newspaper articles and radio broadcasts (Shama, 2008), and the authorities in Britain and the United

States found themselves having to explain why this miraculous new drug was being reserved exclusively to meet military needs and was unavailable to the civilian population.

This work is primarily concerned with how information about penicillin came to be diffused amongst scientists in Europe. This includes both those at academic institutions as well as those in industry and particular emphasis is placed on the countries of Germany, Holland and France. Interest in penicillin was based on its therapeutic potential and if this were ever to be realised it naturally implied production of the antibiotic. Therefore, in addition to tracking information transfers and exchanges *via* the medium of articles in learned journals, it is necessary also to consider transfers of a somewhat more tangible sort: cultures of penicillia – the *sine qua non* of penicillin production.

Despite the war researchers in Britain and the United States continued to publish their findings on penicillin almost without any form of control or censorship. The exception to this was studies relating to the determination of the chemical structure of penicillin and those intended to achieve its chemical synthesis (Anon., 1947). This was largely as a result of perceived German superiority in organic chemistry.

II. Early Penicillin Research in Great Britain

The precise circumstances by which Alexander Fleming came to isolate his celebrated mould are not known nor indeed is the exact date in time when this event occurred. Naturally enough this has led to all sorts of speculation and ultimately to a forensic-like reconstruction of the most probable sequence of events that led to the isolation (Hare, 1970). Even Hare's work convincing as it is, is predicated to a very great extent on statements made when Fleming had achieved fame and was himself trying to piece together events that had occurred some 15 years or more earlier, and so should not be thought of as definitive (Root-Bernstein, 1989).

Sticking to verifiable facts, having isolated the mould, Fleming took steps to preserve it, determined the antibacterial spectrum of the active principle that he termed 'penicillin' and published an account of his findings in the *British Journal of Experimental Pathology* in 1929.

Fleming had been unable to extract and purify the penicillin from the crude broths in which the mould, a strain of *Penicillium notatum*, had been cultivated. This impasse was also encountered by what may be referred to as the 'first wave' of researchers who attempted to further investigate Fleming's observations. These were Harold Raistrick at the London School of Hygiene and Tropical Medicine (Clutterbuck et al., 1932) and Roger Reid at Penn State University (Reid, 1933, 1934). Thanks to Bennett and Chung (2001) the name of another penicillin pioneer, Bornstein (1940) has recently been brought to light.

There can be little doubt that Fleming's interest in penicillin waned in the years following his initial description of the antibiotic. However, it did not dry up altogether: working from Fleming's laboratory notebooks, Wainwright (2002) has ingeniously attempted a reconstruction of a paper that Fleming might have written, and which he speculates may even have been submitted, but not accepted, for publication.

If Raistrick and Reid could indeed be considered the first wave, the second wave was to be of tsunami-like proportions. In 1938 Howard Florey and Ernst Chain at the Sir William Dunn School of Pathology at Oxford University began a study of microbial antagonism. Having conducted an extensive literature review of the phenomenon, they narrowed their field of interest to three compounds; these were a bacteriolytic agent produced by *Bacillus subtilis*, pyocyanase and penicillin (Macfarlane, 1984). Pyocyanase proved to be too toxic to animals and therefore they turned to penicillin.

Chain was a skilled biochemist and he was soon able to extract and purify penicillin from crude mould broths. This permitted the Oxford workers to undertake crucial *in vivo* experiments. The results they obtained were to prove a dramatic testament to the chemotherapeutic powers of penicillin against deadly bacterial pathogens. Florey and his co-workers published their initial findings in *The Lancet* in August 1940 (Chain et al., 1940).

The potential that penicillin held in a time of war was certainly not lost on Florey, and he set about organising the manufacture of the antibiotic on a scale sufficient to permit clinical trials. However, if he had had no qualms about publishing the first of his first results in *The Lancet*, something happened to make him think again before making any further disclosures. Sometime in the spring of 1941 Florey was written to by the Swiss pharmaceutical firm Ciba requesting a culture of *P. notatum*. He saw in this request the possibility that the culture might be passed on to Germany, and this was something he was evidently determined not to let happen. Florey took immediate action, he knew that Fleming would have cultures, but so too would the National Collection of Type Cultures (NCTC) and he wrote to Sir Edward Mellanby of the Medical Research Council (MRC), under whose aegis the NCTC came, as well as to Fleming.

In his response, dated 23rd April 1941, Mellanby admitted that Florey had raised ‘a matter of some difficulty.’ Mellanby could not see how he could instruct the NCTC not to send out cultures to a neutral country such as Switzerland. But Mellanby did not see this as serious matter, assuring Florey that he was ‘miles ahead of any possible competition.’ Fleming replied on 25th April 1941. ‘I am entirely in agreement with you that we should not pass on cultures of the penicillium to the enemy, and if Ciba, or any similar firm, approach me I will refuse.’ He went on to write: ‘During the past ten years I have sent out a very large number of cultures of penicillium to all sorts of places, but as far as I can remember none have gone to Germany. In this country many people have (or had) cultures, including places like Burroughs Wellcome, Evans Leischer & Webb, May and Baker, Parke Davis, and Boots. It is unlikely that they would be approached, but it possible that an application might be made to Raistrick who has written on the subject. I have talked to Raistrick on the telephone and he agrees that, seeing we are at war, he will not supply cultures to Ciba’.

Fleming’s response is revealing, and its wider implications have not been fully appreciated. Quite apart from the early industrial interest, it has become almost the convention to stress how little impact Fleming’s 1929 paper had had. Yet Fleming states categorically that he had sent out ‘a very large number of cultures’ to various persons and organisations. This was evidently in response to requests from those who had read his article or otherwise heard about penicillin.

But returning to Florey, the responses he had received from Fleming and Mellanby evidently re-assured him and he went on to publish in August 1941 the second of his

Lancet papers on penicillin (Abraham et al., 1941). This paper contained all that was then known about culturing the mould and extracting and purifying the penicillin. Apart from Chain's masterful contribution, it owed much to the experimental ingenuity of Norman Heatley. Florey must have felt secure in the knowledge that without the mould no one in Germany could undertake production despite having what was in effect a blueprint for small scale manufacture.

It is interesting to reflect on Florey's attitude to Germany and the Germans. As has already been mentioned, Florey was to undertake what was to become virtually a one man mission to recruit the combined resources of the British and American pharmaceutical industries in achieving mass production of penicillin. Another facet of this crusade of his appears to have been an equally strong determination to deny the benefits of penicillin to the enemy. Florey never quite lost his anxieties about the possibilities of Swiss-German collusion; when he was contacted by the Red Cross on 21st October 1942 for information on penicillin he declined to supply it responding curtly that work was at an experimental stage and that it was 'very improbable that [penicillin] will be available in any quantity for the general public or for such an organisation as the Red Cross for a very long time to come.' Also, during the war Ian Fraser was sent to Oxford to receive instruction from Florey himself on the administration of penicillin in the forward battle area, Florey suggested to Fraser that he should not give penicillin to German wounded, something that Fraser absolutely refused to accept. (Fraser, 1995).

III. Germany

The war had an obvious impact on the exchange of scientific information between countries by what might be called the normal channels of communication. Books and journals published by enemy states suddenly became unavailable. Germany took steps to access firstly British publications denied to them because of the war, and then with the United States' entry into the war, American publications. Similar measures were later put in place by the United States. The details of these information-gathering operations have been extensively documented by Pamela Spence Richards in a number of publications and the following two paragraphs draw heavily from Richards (1994).

Immediately after September 1939 the German government put into action a carefully prepared operation for the collection of foreign journals. German scientific attachés in neutral countries such as Sweden, Portugal, Turkey and Mexico obtained copies of journals and had them shipped to Germany in diplomatic pouches. These publications were forwarded to the Emergency Association of German Science at the Preussische Staatsbibliothek from where they were forwarded to the Technische Hochschule in Berlin-Charlottenburg where a special photographic unit reproduced them by photostat or microfilm. Copies of articles or whole issues of journals were then distributed to the relevant research institutions and to reviewing organs such as *Chemisches Zentralblatt*, *Physikalische Berichte* and the medical reviews produced by Springer.

Well planned as this scheme was, the intensification of the war soon began to hamper the process of acquisition particularly once the United States had joined the conflict. Interruptions to the flow of foreign scientific publications into Germany were evidently seen as having a negative impact on the German war effort, and the state intervened to remedy the situation. In 1941 a new organization was formed, the German Society for Documentation, which came under the direct control of the Minister of Education. One of this organisation's most useful achievements was to publish in December 1943, an

inventory of all foreign journals imported into Germany since September 1939 including, most crucially, details of their precise locations in the country.

In addition to these arrangements, there were also in operation unofficial channels by which foreign articles might be acquired. German industry evidently had its own networks for getting hold of Allied scientific publications. Unsurprisingly, material that was of particular commercial interest was sometimes withheld from potential competitors. Indeed Richards documents a case of a complaint being made to Goebbels's ministry that certain companies and research institutes were keeping the best new acquisitions for themselves.

Despite these arrangements there would inevitably have been delays in the distribution of enemy material to those most qualified to assess and exploit it. Florey's *Lancet* papers did reach Germany and once they did so it is not inconceivable to imagine that a search was instigated for a culture of Fleming's mould. And Fleming was wrong: he had sent a culture of *P. notatum* to a least one person in Germany. This information first came to light in Allied intelligence reports compiled immediately after the defeat of Germany. Teams of Allied scientists followed in the wake of the advancing armies with the objective of uncovering German research and development that had taken place during the war. There were priority areas such as advances in weapons technology, and nuclear weapons in particular, but every facet of German science and technology was to come under scrutiny. The teams came under the auspices of a number of different organisations and there was much duplication of effort. The two organisations of relevance here are the Combined Intelligence Objectives Subcommittee (CIOS) and British Intelligence Objectives Subcommittee (BIOS).

The recipient of Fleming's strain was referred to in the CIOS and BIOS reports simply as 'Dr Schmidt' who was at the IG Behring works at Marburg and at least 3 visits were made to the IG Behring works. It seems that Schmidt had obtained the culture at an unspecified time before the war but had not attempted to culture it. When Schmidt was finally called to perform his patriotic duty he was unable to coax the culture to grow. He passed it on to microbiologists at Berlin-based pharmaceutical firm Schering, but they too failed to grow it and must have concluded that it had lost its viability in the years that Schmidt had stored it.

There was, however, an obvious source to which one might turn to for cultures of penicillia: the fall of Holland in May 1940 had delivered into German hands what was undoubtedly the greatest mould collection in the world. This was the Centraalbureau voor Schimmelcultures (CBS) located in Baarn near Utrecht.

Shama and Reinartz (2002) had previously speculated that the time when German scientists found out about penicillin was in the autumn of 1942. This date was arrived at from letters that were received at the CBS from Germany. However, a recent discovery of a letter from the CBS archives now suggests that the actual date may have been earlier. The letter, from the Dutch offices of Bayer in Amsterdam and dated 3rd August 1942, refers to earlier correspondence of February and March of the same year. It is a reminder; the CBS appear to have promised to send a new strain of *P. notatum* to Professor Dr H Schmidt of the Marburg works, and the letter is to inform the CBS that it is now urgently required. This must be the same Dr Schmidt referred to in the CIOS and BIOS reports. The letter goes on to stress the urgency of the request and mentions Fleming and penicillin by name. If this was indeed the first request to the CBS, by

working backwards it enables some estimate to be made of the interval of time that elapsed between the appearance of Florey's first article on penicillin (August 1940) and the same article landing in Schmidt's lap. If the date of Bayer's Amsterdam office first letter to the CBS is taken as February 1942, then this represents a delay of 18 months. If one allows a period of two months to cover first Schmidt's, then Schering's failed attempts to culture the strain, then a more realistic estimate of the delay would be 16 months.

The CBS was subsequently to receive numerous requests from Germany for *Penicillium* cultures. The first wave was received towards the end of September 1942 but a steady trickle continued more or less continuously until well into 1944. News was evidently spreading throughout the German pharmaceutical industry. Any prospective purchaser of cultures from the CBS would almost certainly have turned to their latest catalogue of cultures. This was the List of Cultures published in 1937 and the Supplementary List of Cultures dated 1938. Neither contained reference to Fleming's strain, *Penicillium notatum*, NCTC 4222. However, listed was *P. notatum* (Westling), and it was for this strain that German organisations applied for. This is indicative that at some stage scientists in Germany reached the conclusion that the CBS did not possess Fleming's strain and that they would try the next best thing.

The requests for *P. notatum* (Westling) came from a variety of organisations and seem to have included virtually every German company, research institute and university with even the slightest connection with pharmaceuticals. Amongst the more well known names are IG Farben in Frankfurt-am-Main, and also at Elberfeld, The Kaiser Wilhelm Institute for Medical Research and Chemistry, the director being the accomplished organic chemist Richard Kuhn.

The crucial question is whether *P. notatum* (Westling) produced penicillin. It may originally have done so, however, repeated subculturing since its deposition at the CBS probably just after 1911 for the purposes of maintenance would have meant that the trait would have not been preserved as it pre-dated even Fleming's work (R.H. Sansom, personal communication, 2001).

Shama and Reinartz (2002) had previously stated that the CBS did not possess the strain at the time. However, new information has come to light that suggests that this assertion may have been incorrect. The information comes from letters exchanged between the Postal and Telegraph Censorship Department and R. St. John-Brooks the Curator of the National Collection of Type Cultures in June 1944. A culture of *P. notatum* NCTC 4222 which St. John-Brooks had sent to the Sociedade Industrial Farmaceutica in Lisbon was intercepted by the Censor and returned to the NCTC. St. John-Brooks wrote to the Censor claiming that he 'did not know that there was any embargo on the sending of cultures of Sir Alexander Fleming's strain of *Penicillium notatum* out of this country. This particular strain was without doubt, widely distributed on the continent before the war as it was sent to Holland in 1930 and was indeed correctly named there by Professor Johanna Westerdijk, Director of the Centraalbureau voor Schimmelcultures at Baarn on 9th April of that year.' It is interesting that despite Mellanby's protestations to Florey that he was powerless to influence the NCTC an embargo was in fact imposed. Table 1 shows the organisations to whom St. John-Brooks claimed to have sent cultures of *P. notatum* NCTC 4222 to.

It now seems very likely that the CBS did after all have a culture. Moreover, the curator of the CBS, Professor Johanna Westerdijk may have been the first to correctly identify it as *Penicillium notatum*. In his original paper Fleming thanks 'our mycologist, Mr la Touche, for his suggestions as to the identity of the penicillium' (Fleming, 1929). La Touche was famously incorrect in his identification; he had proposed *Penicillium rubrum*, and Macfarlane states that Raistrick was doubtful of the identification and sought the advice of the great American mycologist Charles Thom sending him a culture on 14th May 1930 (Macfarlane, 1984) *after* that received by Westerdijk.

Applying to the CBS for cultures of penicillia was one strategy, the other was to attempt isolation of strains of penicillin-producing strains of *Penicillium*. This was indeed put to effect at a number of laboratories throughout Germany. These efforts first came to light in a series of intelligence reports that were mentioned above and are described in greater detail in Shama and Reinartz (2002). Previous to this particular study, German activities in the field of penicillin research had been described in work published in German an excellent example being (Pieroth, 1992).

Some German workers, notably Hans Knöll at the Schott Glass works did succeed in making penicillin. It was never to have nothing like the impact that the Anglo-American initiative was to have. This was due to a number of factors; the first was the lack of any central co-ordinating authority. This would have been essential, as different strains would have needed to be compared with one another using standardised assays for penicillin so that the most productive could be cultured industrially. As the war progressed, the frequency and destructive power of Allied air raids over Germany increased. Any novel industrial process developed on a sufficiently large scale would have therefore drawn the attention of Allied military planners who would have singled it out for destruction. Similar fears had led Florey to seek American industrial help in mass-producing penicillin simply because American plants would have been beyond the reach of the Luftwaffe. When finally the need for a coordinating committee was appreciated by German researchers and a meeting called in Berlin in October 1944, the stark realisation was made that it was already too late as the necessary raw materials and plant necessary would never be made available (Shama and Reinartz, 2002). The diverse and disparate attempts to isolate penicillin-producing moulds would almost certainly have led to the isolation of novel antibiotic compounds; an example being the work of von Kennel et al. (1943). Some of these compounds would undoubtedly have had therapeutic worth, whilst others would have proved themselves toxic and of no practical value.

The apparatus put in place by the German authorities to acquire Allied scientific and technical material was described above in some detail, and it is therefore interesting to gauge its efficiency towards the latter stages of the war. An article on penicillin appeared in a journal entitled *Chemiker-Zeitung* in October 1944 (Loewe, 1944). The journal appears to be aimed primarily at industrial chemists and engineers, and the article itself is a review of the status of work on penicillin. Despite mention in the Introduction of an embargo on publication of studies relating to the chemical structure of penicillin, some early proposals e.g. Abraham et al. (1942) and Catch et al. (1942) were in fact published before the embargo was imposed. Both proved to be incorrect but Catch et al.'s work is cited in Loewe's review. German workers, this article reveals, had become acquainted with the fact that penicillin was being made in the United States by submerged culture and that corn steep liquor was being used in its manufacture. The latter was apparently unknown in Germany, for it has been mis-translated as 'maisalkohol' i.e. grain alcohol.

Information is provided to the journal's readership on the War Production Board and the names of all the American pharmaceutical companies involved in mass production. The latest American work cited dates to the latter part of 1943 and includes *Science* (July, 1943), *Oil, Paint and Drug Reporter* (July 1943), *Chemical and Engineering News* (September, 1943). The range of material is impressive but the elapse of time between publication in the United States and its arrival into the right hands in Germany is just over 12 months. Apart from Swiss articles dating to 1944, the article contains a citation of a piece of French work from January 1944 (Nitti, 1944) which is considered below.

Richards (1994) did not consider the Swiss contribution to German information gathering initiatives. As a neutral country, British and American publications would have been more readily available than in most of the rest of Europe. As a country having a sizeable pharmaceutical industry, publications on penicillin would have had particular interest. This led to the publications of reviews (e.g. Wettstein, 1944) that would have been readily obtainable in Germany.

Despite the attempts described above and the 'near miss' with the Dr Schmidt's culture, the German authorities never quite gave up the quest for a culture of Fleming's mould. An American agent, Hamilton Southworth, visited the Pasteur Institute just after the liberation of Paris and was told that there persisted attempts to obtain Fleming's strain until as late as June 1944.

But the story of Fleming's strain of *P. notatum* in Germany does not end there. There had been at least one other microbiologist in Germany with a culture of this particular organism – at least until the year 1933. Julius Hirsch had obtained his PhD under the pioneer biochemist Carl Neuberg (1877-1956). At some stage in his early career Hirsch worked for a period of two years in London with D.D. Woods and H. McIlwain and acquired a culture of Fleming's mould whilst in London. He returned to Germany and was appointed Professor at the University of Berlin (Bartmann and Wagner, 1962) but because he was a Jew was deprived of his post in 1933. Although she does not specifically mention Hirsch, the expulsions of Jews from academia in Nazi Germany has been described by Deichmann (1999). Hirsch managed to escape to Istanbul where he became a Professor at the Institute of Hygiene. He evidently took his strain with him because he published some accounts of his work with the mould (Hirsch, 1944). This article serves to indicate how Hirsch had access to surprisingly up to date information in Turkey. In addition to revealing familiarity with the names Florey and Raistrick, Hirsch cites an article published in *The Times* on 12th February, 1944. Hirsch's work came to be recognised outside of Turkey; his studies of a glucose oxidising enzyme that possessed bacteriostatic properties produced by *P. notatum* (Fleming) was mentioned in the Editorial of *The Journal of the American Medical Association* in March 1944 (Anon, 1944). This work of Hirsch's on this particular enzyme, which came to be known as notatin, was also cited by Coulthard et al. (1945). It is interesting that these authors betray their incredulity that Hirsch could actually be in possession of Fleming's culture, for they state "Hirsch (1943) observed the secretion of a glucose-oxidising enzyme by *P. notatum* Fleming (*sic*)..."

A most curious aspect of this particular chapter of the history of penicillin is just what Hirsch considered to be vital to him as he fled his country of birth for Turkey. Had he left behind his precious culture of *P. notatum* in Germany someone might have found it and German penicillin production would have taken a very different turn. The final irony perhaps being that Hirsch's work on notatin was cited in the article by Loewe (1944) mentioned above.

Work published some 25 years ago reveals an interesting example of sharing of information between wartime allies. Manfred Kiese of Berlin University wrote a review on penicillin in which he abstracted articles that had appeared in Britain and the US, including of course *The Lancet* articles. These were published in *Klinische Wochenschrift* in the issue of 7th August 1943 (Kiese, 1943). In his review of the early history of antibiotics in Japan, Yagisawa (1980) makes reference to a certain Mrs Fusako Tsunoda who conducted research to show that this issue of the *Klinische Wochenschrift* was actually conveyed to Japan by submarine which she managed to identify as 'I-8' which left the port of Brest 5th October, 1943 and arrived in Kure near Hiroshima on 21st December of that year.

Yagisawa also (1980) mentions a Professor Masahiko Kuroya at Tohoku Imperial University who was active in penicillin research and he coincidentally was also the subject of an intercept by the Australian Special Wireless Group made on 18th September 1944 and sent to Florey for information. The message claims that Kuroya and his assistant Shikaji Kondo had discovered 'a new type of penicillin with surprising curative effects over Fleming's penicillin.'

IV. Holland

The strategy adopted by a number of German organisations in contacting the CBS for cultures of *P. notatum* and described above would of course have alerted the staff there to the interest in this particular mould. Some of the requests for cultures sent by post from Germany specifically refer to Fleming. The latter's original paper on penicillin would have been available in academic libraries in Holland even though Florey's *Lancet* papers would not have been.

The Director of the CBS was the redoubtable Johanna Westerdijk. Westerdijk had commenced her studies in botany at Amsterdam University in 1900 before going on to study in Munich and then Zurich from where she obtained her PhD. She was appointed to a chair in botany at Utrecht University in 1917 so becoming the first woman professor in Holland (Ten Houten, 1963). Under her leadership the CBS expanded greatly becoming arguably the finest in the world. In her position as Director Westerdijk would have therefore been supremely placed to inform fellow Dutch scientists of German interest in penicillin. The question of whether she did or not is considered below.

Reference has already been made to teams of Allied technical specialists who followed in the wake of the armies as they swept through mainland Europe. Their mission was not confined to Germany and they interviewed a number of scientists in Occupied countries as they became liberated. Between 6th June and 5th July 1945 at least three teams were charged with uncovering medical research in Occupied Holland. Each of them seems to have interviewed Professor JV Konigsberger. These reports contain much common material and the following is a distillation of the most important revelations contained in them.

Konigsberger carried out the clandestine production of antibiotics in Utrecht. This work was centred on *P. expansum* that produced an antibiotic that he termed 'expansine' but was in all probability patulin. Expansine proved to be too toxic for systemic use but had some value for treating fungal infections of the skin. Konigsberger was not under any

misapprehension that he was working with penicillin. That this can be asserted is due to the following. Koningsberger admitted contact with Dr J.J. Duyvené de Wit who was in charge of research at the pharmaceutical firm of Brocades, Stheeman and Pharmacia. Stheeman was closely involved with an activity for making penicillin in Delft at a company known as the *Nederlandische Gist en Spiritusfabriek* (NG&SF) and described in recent work (Burns and van Dijck, 2000).

Workers at NG&SF managed to get hold of a German review of penicillin mentioned above (Kiese, 1943). However, they obtained an additional source of information by a remarkable incidence of serendipity. Andries Querido had been associated with the company, but because he was Jewish, came to be interned at Westerbork transit camp in January 1943. The Germans appear to have conferred a 'reserved occupation' status on workers at the plant, and this evidently extended to Querido. He was allowed visits to the works at Delft but was obliged to leave behind his wife and children as hostages at Westerbork. At Amsterdam station he encountered by chance S. van Creveld, a senior lecturer in child health at Amsterdam University. Van Creveld told him about a 'Swiss medical journal' (almost certainly the *Schweizer Medizinische Wochenschrift*) dealing with 'a miraculous new compound – penicillin'. Van Creveld lent Querido the article and Querido took it to the Gist works where a programme for producing penicillin came to be initiated (Querido et al., 1990)

Returning to Koningsberger, he also revealed that he had heard about penicillin from an RAF leaflet that had come into his possession. Shama and van der Els (2008) have recently speculated that the leaflet might have been one belonging to a series known as *Wervelwind* i.e. Whirlwind, dropped over Holland on the night of 24th/25th April 1944 (see Figure 1). Finally, Koningsberger stated that he had a copy of the *Schweizer Medizinische Wochenschrift* of June 1944, and therefore would have known from this source the identity of penicillin-producing strains. In the course of his interviews Koningsberger made reference to fellow scientists with whom he was involved. Apart from the mention of Duyvené de Wit, there was also Dr B.C.P. Jansen, Director of the Laboratory of Physiological Chemistry, Netherlands Institute of Nutrition, Amsterdam, and Abraham van Luyk. The latter had been working alongside Koningsberger since 1940. Before that van Luyk had been Westerdijk's assistant from 1910 until his retirement from the CBS in December 1939 (Faasse, 2008 p141). The interesting omission is Johanna Westerdijk. Despite this Koningsberger was aware that 'two or three dozen German institutes had obtained stains [of penicillia] from Baarn [i.e. the CBS]'

Koningsberger may have come across this information from van Luyk who, following his long service at the CBS, would almost certainly have maintained contacts there. Koningsberger and Westerdijk must have known each other well. Baarn is after all only a few miles from Utrecht. Faasse (2008) points out that Koningsberger and Westerdijk would have had occasion to meet formally at least once a year as both were on the board of the CBS. Faasse also states that Westerdijk corresponded with Koningsberger whilst the latter was temporarily interned. Possibly Koningsberger disapproved of her meeting requests from Germany for strains of penicillia. Possibly too he sought to prevent the knowledge of his own clandestine activities coming to the attention of the Germans, and only confided to those with whom it was strictly necessary to do so. It is however strange that with the world's greatest mould collection on his doorstep Koningsberger should choose to isolate his own strains of *P. expansum*.

Westerdijk was herself in a difficult position: she could hardly refuse to send cultures to Germany. Occupying a position of authority she must have been aware of the possibilities that amongst the people she came into professional contact were those who might denounce her to the Germans in order to secure preferment. According to Faasse (2008) one manifestation of such a threat at the CBS was Dr F H van Beyma thoe Kingma who demonstrated collaborationist tendencies, and who was apparently able to travel freely to Germany. Huub van der Aa, a onetime employee of the CBS, has in his possession letters revealing that plans were being considered to remove the entire CBS to Germany. Van Beyma thoe Kingma was apparently party to these discussions. These plans never materialised, partly it must be assumed, because of the objections of German researchers such as Hans Knöll who argued against the practicality of such a scheme. Notwithstanding, it seems likely that Westerdijk had at least some inkling of these plans and this might have activated her conduct towards German agencies.

Following the liberation of Holland persons in positions of authority were obliged to account for their wartime conduct. In the first instance this comprised a questionnaire containing such questions as: 'have you accepted any new position during the occupation? Have you taken over the duties of anyone who had lost his position as a result of a German measure? Westerdijk had to submit to this process, and her answers to all of the above were in the negative. When asked whether she had maintained contact with Germans for the benefit of her academic work, she replied that she had kept contact with Professor G Gassner of Magdeburg University (Faasse, 2008).

There is in the Florey archive one piece of evidence that suggests that Westerdijk's contacts with German scientists went deeper than she was prepared to admit. The document comprises intercepted intelligence material sent to Florey for information by a certain Dr John Barnes at Porton Down. The documents are dated July and August 1944. This material reveals that Westerdijk was in correspondence with Professor Eugen Haagen of the University of Strasbourg and also Chief of the Luftwaffe Medical Service, over penicillin production by various strains of penicillia. Westerdijk had apparently carried out assays for Haagen. Just how Barnes came across this intelligence is unclear. He formed part of a unit known as ALSOS charged with monitoring German capability to produce biological warfare agents¹. The unsavoury fact was that in addition to his sideline in antibiotics, Haagen was also carrying out typhus experiments on human inmates of Natzweiler-Struthof concentration camp. He was eventually indicted with war crimes and sentenced to 20 years imprisonment, but never served more than a couple of years (Baumslag, 2005). Naturally Westerdijk would not have known any of this.

The strains mentioned in the intelligence report were *P. notatum* (Westling), *P. puberulum* (Bainier), *P. corylophilum* (Dierckx) and *P. expansum* (Link) - none of which produce penicillin. Westerdijk's responses cannot have satisfied the authorities, for she was summoned to appear before the Committee for the Restoration and Purification of Utrecht University and suspended from giving lectures. A flavour of what course the interview took can be gauged from an unsigned and undated note that Faasse came across in Westerdijk's case file.

'After reports of the American penicillin research had reached the Netherlands and Germany, German researchers tried to produce the magic remedy. The Dutch research

¹ This information was provided by G.B. Carter author of Chemical and Biological Defence at Porton Down, 1916-2000, published in 2000 at The Stationary Office, Norwich.

effort in this area went underground. The Germans contacted the CBS and demanded strains of the fungi *P. notatum* and *P. expansum*. Westerdijk had sent them these strains after first checking that they had lost the power to kill bacilli. The Germans had been unable to get anywhere with these strains.’

The Committee considered the evidence and came to the conclusion that Westerdijk had not taken action that that was of significance to the German war effort. She was allowed to resume her lecturing on 20th September, the Committee writing to her that ‘Albeit that we can appreciate the factors that caused you to take up the position you adopted, we nonetheless share your own feeling of regret that you did not display a spirit of resistance such as might have been possible, even in your circumstances.’

Reference to newly discovered documentary evidence discussed above strongly points to the CBS possessing a culture of Fleming’s strain of *P. notatum*. If she did indeed possess this strain it seems that she did not hand it over. This was in itself an act of resistance that needs to be acknowledged.

The question of whether or not Westerdijk informed fellow Dutch scientists about penicillin must remain open. It seems strange that if she did possess Fleming’s strain she did not pass it on to the *Nederlandische Gist en Spiritusfabriek*.

Florey seems either to have forgotten about the intelligence he had received of Westerdijk’s communication with Nazi officials, or considered it to be insignificant, for after the liberation he replied to a letter of hers on 20th September, 1945 stating that he was ‘delighted to hear that your great fungus collection has been kept going.’

V. France

For a long time an image existed of the French population during the Second World War as standing united in resisting their German occupiers. Naturally this has been proved to be a myth. Studies appearing over the last 30 years or so paint a rather less heroic reality. All sorts of accommodations had to be arrived at with the Germans both at the level of the individual and of organisations. This is not of course to diminish in any way the heroic few who refused to enter into any compromises whatsoever and chose to resist to the end.

Conflicts of this sort were being played out at the Pasteur Institute. During the occupation it was obliged to produce therapeutic sera for export to Germany whilst at the same time serving as a secret store of medical supplies that were put at the disposal of French resistance movements (Chevassus-au-Louis, 2007). Some of the workers at the Institute, such as Ernest Fourneau, came to be charged with collaboration after the war had ended (Chevassus-au-Louis, 2004), whilst others such as Federico Nitti, came to be decorated for the acts of resistance they performed.

The systems in place for accessing foreign publications in France during the war years have been documented by Richards (1994) and also serve as an example of this duality. One system that was put into operation represented what, according to Richards, was an example of successful scientific co-operation and resulted in the exchange of journals between France and Germany. The driving force behind this particular initiative was Jean Gérard, Secretary General of the Maison de la Chimie. As such he was director of

one of the best scientific periodical collections in the world and, moreover, its microfilming facilities were considered amongst the best in existence. Gérard was able to reactivate the Maison's subscriptions to German journals that had been cut off by the terms of the Armistice. The scheme was fairly successful but was ultimately limited to the material that Gérard's German contacts had access to, and whilst material from certain countries was readily accessible, that from other countries including the United States, soon fell into short supply. Richards's own assessment of Gérard is that while he performed valuable services to the Germans by thoroughly indexing French scientific publishing during the occupation, and by making German research available for French scientists, she found no evidence that he provided access to Allied science that the Germans did not already have.

Richards also describes the existence of a clandestine channel that provided French scientists with access to Allied research. An illegal indexing and abstracting service was operated throughout the period of the occupation by the Centre National de la Recherche Scientifique (CNRS). In this case the leading personality was Frédéric Joliot-Curie. At the beginning of 1941 Joliot-Curie asked a young scientist, Jean Wyart, to take over the embryonic documentation service started by the CNRS in 1939. Despite the division of France into free and occupied zones, Wyart was able to travel freely between the two, and as a result, access both British and American material.

A rivalry developed between Gérard and Wyart. This had consequences for Wyart because only Gérard had the authority to distribute paper for documentation purposes and he used that power to deny Wyart paper. However, printing – only possible with German permission – was arranged through an acquaintance of Wyart's, the head of the prestigious Hermann Scientific Editions. Thus was produced the CNRS's *Bulletin Analytique* that appeared monthly, offering three- to six-line summaries of French, British, and American articles and the possibility of ordering the original on microfilm.

Curiously the Germans made no efforts to suppress the illegal index, despite the protestations of Gérard, with whose service it was competing successfully because of its British and American content. Richards does not consider that this tolerance was in any way due to the German's need for the index as they already had an efficient system of their own as described above. She considers that its very nature and low audience must have made it a low priority for the Germans.

Florey's papers may well have entered France by one of the routes described above. However, Quirke (2008) states that the French pharmaceutical company Rhône-Poulenc obtained 'English technical reports' at the end of 1942, and that these were probably Florey's *Lancet* papers. The approach that Ciba had made to Florey in April 1941 was described above; it is conceivable that news about penicillin may have circulated amongst the industrial pharmaceutical community in Switzerland. This would have included both Swiss companies as well as foreign companies with offices in Switzerland. Included amongst these was Rhône-Poulenc². The possibility exists that Rhône-Poulenc employees may have learned about penicillin from their counterparts in Ciba and then have passed the information on to their parent company in France.

Some indication that information exchanges of this kind did occur within pharmaceutical circles is evidenced by a small wave of requests for *P. notatum* (Westling) that arrived at

² Personal Communication by V. Quirke see also Quirke (2008)

the CBS in Baarn starting in the summer of 1943. Indeed one can track the sequence by which news about penicillin spread. The first of these was from the Laboratoires du Dr Roussel (7th July 1943), followed by the Etablissements Byla (23rd September, 1943) and finally Maison L Frere (3rd February, 1944). Missing from this list is Rhône-Poulenc and the reason for this must be that they already had access to Fleming's strain of *P. notatum*.

Rhône-Poulenc had a natural collaborator that they would turn to once they had copies of Florey's paper in their hands; this was the Pasteur Institute. They had previously worked closely together on research into novel of sulphonamides, and indeed, the then director Jacques Trefouël had been instrumental along with Nitti in unravelling the mode of action of these antibacterial drugs. Most important of all for Rhône-Poulenc was the fact that the Pasteur Institute possessed a strain of Fleming's *P. notatum*. This was according to Quirke (2008) presented to the Institute by Fleming himself when he visited Paris, or alternatively, according to the testimony of one Bernard Sureau, to whom we shall return, presented to André Lwoff by Fleming when Lwoff visited London. Quirke also states that Raymond Paul, Research Director at Rhône-Poulenc warned Nitti in late August 1943 that they should not fall behind in the penicillin race. She even mentions that the possibility that collaboration with Professor Hörlein Director of the Bayer laboratories had been considered. The possibility cannot, therefore, be ruled out that Florey's papers may have reached Rhône-Poulenc directly from Germany. Certainly, the date that Quirke quotes 'the end of 1942' falls after the time when news about penicillin had reached German scientists.

Production started on a small scale at Rhône-Poulenc's site at Vitry but assays were performed at the Pasteur Institute. The French researchers would almost certainly have employed the penicillin assay described in the second of Florey's Lancet papers (Abraham et al., 1941). This was based on the use of small porcelain cylinders impregnated with penicillin solutions and deposited on petri dishes in which the agar had previously been seeded *Staphylococcus aureus*. However, they seemed to have employed an assay that they had devised themselves. This was based on what they termed 'microbiophotometry' (Faguet and Nitti, 1943). The assay made use of a device that was in many ways ahead of its time and that was capable of automatically recording the growth of up to six individual cultures simultaneously. By this method the inhibitory effect of penicillin could be determined by the effect it had on the growth rate of the target organism – presumably cultures of *S. aureus*.

Bernard Sureau who was mentioned above, was during the war a young intern based at the hospital connected to the Pasteur Institute. He worked with Nitti and has left an undated deposition in the archives of the Pasteur Institute that describes his involvement with penicillin. Sureau's account is a personal one but is somewhat at odds with other sources. There is no mention of Rhône-Poulenc in his account; instead Sureau attributes the initiation of penicillin research at the Pasteur Institute to Nitti having heard a BBC French service broadcast in the Autumn of 1943. Shama (2008) has established that there was in fact a French broadcast on penicillin made on 29th September 1943. In contrast to Home broadcasts, those made by the Foreign Services of the BBC were aimed at medical professionals and it is indeed possible that Nitti heard the broadcast and may have obtained useful information from it and even encouragement: it was almost certainly not what initiated penicillin research at the Pasteur Institute. Sureau gives an example of the lengths that the researchers at the Pasteur Institute were prepared to go to obtain Allied literature on penicillin. He claims that a colleague was dispatched to

Spain to acquire a copy of a special edition of *The British Medical Journal* of 15th April 1944 on penicillin.

Sureau also describes an early trial of their penicillin in January 1944 on a young infant dangerously ill with meningitis. Massive amounts of sulphonamides had been given to the infant but to no avail. An immediate improvement occurred once penicillin had been administered but their meagre stock of the antibiotic ran out and the infant succumbed once more to meningitis and finally died. This account bears a number of striking similarities to the first recorded use of penicillin in Oxford (Macfarlane, 1984). The patient was Albert Alexander who was at death's door with a relentlessly spreading infection occasioned from a scratch with a rose thorn. The precious stock of penicillin was administered with miraculous results that turned to tragedy when the penicillin was exhausted. In their desperation the Oxford medical team had even resorted to extracting the penicillin from the patient's urine and re-injecting it into him. In both cases despite the death of the patient those administering it had seen enough to become convinced of penicillin's therapeutic value.

This particular clinical case was to form the basis of a small clutch of publications in French journals. The first of these was by Nitti that appeared in print a matter of weeks after treatment of the infant ill with meningitis (Nitti, 1944). A second paper was to follow in March 1944 reporting on the same case. The authors were Martin, Sureau and Vittoz (Martin et al., 1944) but interestingly not Nitti. A third paper appeared in June of the same year (Martin and Sureau, 1944).

Examining the British and American papers cited in these publications is indicative both of the efficiency of French document gathering procedures and of the time delays that researchers at the Pasteur Institute were obliged to incur. Both Nitti (1944) and Martin et al. (1944) cite Fleming (1929) and Raistrick's work (Clutterbuck et al., 1932) both of which would have existed in Parisian libraries before the war. They also cite Florey's two *Lancet* papers, (Chain et al., 1940; Abraham et al., 1941). The most recent British publication is a *Lancet* paper of 1943 (Clark et al., 1943). They also refer to a German review on penicillin published by Kiese (1943)

Nitti's paper makes reference to Florey's *Lancet* papers and interestingly to a chemical composition for penicillin that seems to be that proposed by Abraham et al., (1942), but is not formally referenced. He also alludes to work of Coulthard's, possibly Coulthard et al., (1942). In addition, he provides his readers with some industrial intelligence – namely that a plant has been established in Canada for the production of 10 kg of penicillin per week. Martin and Sureau (1944) make reference to an article in the *Journal of Bacteriology* of August 1943 –this was almost certainly by Foster and Woodruff (1943). The latter indicates that the delay in obtaining foreign material was just under 12 months.

The researchers at the Institute Pasteur must have published in the knowledge that their work would come to the attention of the Germans. They were possibly ignorant of the fact that no one in Germany possessed Fleming's strain. The true situation would have become plain when German officials turned up at the Institute demanding the strain. Hamilton Southworth, an American agent, who visited the Institute immediately after the Liberation and whose report on the situation prevailing is considered below, was told that about 8 months prior to his visit (i.e. January or February, 1944) – just after Nitti's publication – German officials tried to obtain the Fleming strain but were alleged to have been given a false one. The officials apparently told the researchers at the Pasteur

Institute that they were organizing their own programme. They tried again in June 1944, this time Schlossberger [This might have been Professor H. Schlossberger, of the Hygiene Institute, Frankfurt] had been present. This account is verified to some extent by Bernard (1947). Nitti's paper certainly made its way to Germany, and was cited by in the review article on penicillin (Loewe, 1944) published in *Chemiker-Zeitung* in October 1944 and referred to above.

Hamilton Southworth was attached to the London Mission of the Office of Scientific Research and Development's Committee on Medical Research. He was the author of a weekly newsletter in which he reported on medical developments from Britain. These were not necessarily confined to British advances but also included intelligence material received in Britain from Germany and occupied Europe. In one newsletter (No. 103) dated 2nd September 1944, Southworth reported on a trip to Paris he made between 28th August 28 and 2nd September 1944. Charles de Gaul had marched into Paris just days before on 25th August.

Southworth went to the Pasteur Institute and met Jacques Tréfouël. He wrote: 'They were isolated, discouraged, and without equipment. Most of what they did was a continuation of their old traditions. The Germans asked for a few things like typhus vaccine and tetanus antitoxin but said very little of what they in turn were doing. When the French failed to cooperate, the breach grew even wider. Suspicion even developed between the different French workers as to which of their neighbours might be "un peu collaborateur".' Southworth was given details of their penicillin work and of Rhône-Poulenc's involvement and that they possessed Fleming's strain. He discovered that only about 30 patients had been treated with penicillin. He commented 'most have had staphylococcal infections and the results have been good. Local use has predominated and there is particular enthusiasm for subconjunctival injection in conjunctivitis. We found no instance of the use of penicillin in syphilis, gonorrhea, or more unusual infections.' Southworth was told that Constantin Levaditi, also at the Pasteur Institute, had a strain of *P. corylophilum* DX obtained from Holland. It produced no penicillin and its activity *in vitro* was presumed to be due to notatin. (This incidentally was one of the strains that Westerdijk had assayed for Haagen).

Southworth's analysis is contrasted with that of Pasteur Vallery-Radot (Louis Pasteur's grandson) who wrote the foreword to a compilation of articles detailing French medical research during the war (Hamburger, 1947).

'I was greatly surprised to learn that our good friends in America had never heard of our latest work in medical research. All were convinced that during those years of oppression France had been living coiled around herself and that her spirit had deserted her body.....How could these men carry on with their work, under such seemingly impossible conditions? The equipment of laboratories was deficient, often the gas and electricity were cut off; to obtain the animals for necessary experiments was of the greatest difficulty.

'They themselves led a miserable life, underfed, shivering with cold all winter, their minds beset with anguish. They lived under the constant threat of being deprived of their freedom, worrying about the fate of their friends who were thrown into jail, deported or shot. How could they be successful in their scientific work? And successful they were, in spite of all the torments of servitude, in spite of their physical and moral tortures, of almost overwhelming difficulties, of this wall shutting off France from the outside world,

and in spite of this numbing silence about all countries not included in the German Reich.’

It is the contention here that the ‘wall shutting off France from the outside world’ was not entirely impermeable nor that the ‘numbing silence’ was total.

Southworth’s revelation of the total numbers of patients that had received treatment with penicillin – some 30 in all - ‘The numbers treated were very small and the overall impact on diminishing human suffering would have been negligible and one might justifiably ask ‘was it worth it?’ In normal times researchers at the Pasteur Institute would have found themselves at the centre of research on penicillin. The war ultimately did not prevent their involvement in research on penicillin. Despite the privations the researchers at the Pasteur Institute were working at what today be referred to as the ‘cutting edge’ of antibacterial chemotherapeutics. Their efforts to make penicillin against all odds provided them with valuable experience in the preparation and extraction of penicillin and this was to become of tremendous benefit in the immediate aftermath of the Liberation and until penicillin became available for civilian use. The opportunity to apply their hard-earned skills was an unusual one. Following the liberation of Paris, that city became the centre for a number of Allied hospitals. The American army made the Pasteur Institute a generous and valuable gift; the urine of all servicemen that were undergoing therapy with penicillin. Therèse Tréfouël, also at the Pasteur Institute even published a paper on the process (Tréfouël et al., 1945).

VI. Conclusions

An absolute requirement for penicillin production in the 1940s was access to the most up to date literature and, most crucial of all, Fleming’s culture of *P. notatum*.

Written requests to Fleming for cultures have not survived³, but it is clear from the account given above that Fleming had been distributing cultures of his mould well before Florey had published his papers demonstrating the therapeutic potential of penicillin. Undoubtedly some of those who had obtained cultures in the period between Fleming and Florey – the ‘*inter regnum*’ as Wainwright (2002) has referred to it - had not attempted to actually grow them until Florey’s papers appeared. Moreover, those that did undertake work on penicillin during the *inter regnum*, e.g. Reid and Raistrick, cannot be said to have significantly advanced the study of the antibiotic.

It is unlikely that Fleming lived to know what the full consequences of his acts in distributing cultures were to have. Perhaps he may have divined the reason why neither Florey nor Chain had to approach him for a culture was that he had previously given one to Georges Dreyer, the former head at the Sir William Dunn School of Pathology in Oxford. Fleming would probably would not have known that when Florey and Chain were deciding which antimicrobial compound to study after pyocyanase proved to be too toxic that a certain Miss Campbell-Renton happened to be culturing *P. notatum* just along the corridor from them (Macfarlane, 1984).

Those scientists in Europe involved in research on penicillin were aware of the massive and well-resourced Anglo-American programme to mass-produce penicillin through

³ Kevin Brown, Curator of the Alexander Fleming Museum, St Mary’s Hospital, London

access to British and American publications that the state of war never succeeded entirely in cutting off. Their motives in pursuing their studies can only be guessed at. It would be reassuring to think that amongst them were humanitarian ones. There were undoubtedly others too including an understandable need to retain their professionalism. Perhaps just being able to produce any penicillin at all under straightened circumstances may have represented a victory of sorts. Being able to publicise the fact through journal publications, so representing a hope that just as British and American articles had reached them, their work might reach the Allies, may have heightened the sense of achievement. Some of those who took part in these attempts are destined to remain unnamed and unknown, but perhaps this work has succeeded in salvaging the names of a few that might otherwise have been forgotten.

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Distribution of Penicillium notatum (No. 4222 –Fleming's strain) since the outbreak of war. (to places abroad)

Division of Industrial Chemistry
Council for Scientific & Industrial Research, East Melbourne, Australia.

Indian Inst. of Science.
Bangalore, India

The British Council (for export)

S.A. Brewing Co. Ltd.,
Adelaide, S. Australia.

N.Z. Government, Strand W.C.
(for export)

School of Pathology, T.C.D., Eire.

Aktiebolaget Marvella
Stockholm, Sweden.

Imperial Mycologist, New Delhi, India.

Guinness Brewery, Dublin, Eire.

Dept. of Pathology, Univ. Coll. Dublin, Eire.

Ministry of Agriculture, Belfast, N. Ireland.

Laboratorio Fidelis, Lisbon, Portugal

Alexr. Lipworth Pty. Co., Johannesburg, S. Africa.

Bakubhai Ambalal & Co., Bombay, India.

South African Inst. For Medical Research, Johannesburg.

Clinsearch Laboratories, J'Burg, S. Africa.

Sociedade Industrial Farmaceutica, Lisbon, Portugal†.

Table 1

(Copied from letter sent by R. St. John-Brooks, N.C.T.C on 9th June 1944 to Dr A. N. Drury, CBE, FRS, Lister Institute of Preventative Medicine, Chelsea Bridge Road, London, S. W. 1.

† This last item was sent but intercepted by the Postal and Telegraph Censors Department)

Figure 1. Text of 'Wervelwind' Leaflet Dropped over N. Holland on the Night of 24th/25th April 1944.