

## ROBERT PULVERTAFT'S USE OF CRUDE PENICILLIN IN CAIRO

by

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Alexander Fleming discovered the bacterial effects of a substance diffusing from cultures of *Penicillium* in 1928. His early attempts to purify an active factor were unsuccessful, as were those of Harold Raistrick. It required the energy of Howard Florey and the efforts of Ernst Chain and others to purify penicillin from the broth used to grow the fungus and to test it in a patient in 1941. However, crude filtrates had been used by Fleming in 1932<sup>1</sup> and Cecil Paine in 1930–31 at Sheffield<sup>2</sup> to treat eye infections. Reports of neither of these uses had been published, although Florey knew of Paine's work.<sup>3</sup>

Penicillin became available in 1942 and was talked about as far away as the Middle East—"We now began to hear about the new drug Penicillin, at that time in extremely short supply on all fronts".<sup>4</sup> The first supplies reached the Middle East about August 1942 in the Central Pathological Laboratory housed with the Fifteenth (Scottish) General Hospital at Cairo, commanded by the then-Major R. J. V. Pulvertaft, Assistant Director of Pathology, Middle East.

In the next months Robert Pulvertaft used these small supplies and made his own crude filtrates with success. This work was reported briefly in the *Lancet* of July 1943 and, with details of 15 cases, later in the year.<sup>5</sup> These meagre sources are now supplemented by Pulvertaft's original reports, which are filed in the Public Record Office, Kew, England, and which show that previous accounts by Alexander Maurois, Peter Baldry, Lawrence Garrod, and Howard Florey et al<sup>6</sup> do not tell the full story. Pulvertaft, working with small supplies of penicillin, was the first to show

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<sup>1</sup> R. Hare, 'New light on the history of penicillin', *Med. Hist.*, 1982, 26: 1–24.

<sup>2</sup> J. Howie, 'Penicillin: 1929–40', *Br. med. J.*, 1986, 293: 158–9; M. Wainwright and H. T. Swan, 'C. G. Paine and the earliest surviving clinical records of penicillin therapy', *Med. Hist.*, 1986, 30: 42–6.

<sup>3</sup> H. W. Florey, E. Chain, N. G. Heatley, M. A. Jennings, A. G. Sanders, A. P. Abraham, and M. E. Florey, *Antibiotics*, vol. 2, Oxford University Press, 1949.

<sup>4</sup> A. D. Morgan, 'The Fifteenth Scottish', in A. P. Milne (ed.), *Aberdeen Medico-Chirurgical Society: a bicentennial history 1789–1989*, Aberdeen University Press, 1989, p.58.

<sup>5</sup> R. J. V. Pulvertaft, 'Bacteriology of war wounds', *Lancet*, 1943, ii: 1–2; *idem*, 'Local therapy of war wounds. 1. With Penicillin', *ibid.*, pp. 341–6.

<sup>6</sup> A. Maurois, *The life of Sir Alexander Fleming*, London, Jonathan Cape, 1959, pp. 179–80; P. Baldry, *The battle against bacteria*, Cambridge University Press, 1976, p. 113; L. P. Garrod, 'Penicillin', in V. Z. Cope (ed.), *Medicine and pathology*, London, HMSO, 1952, pp. 551–60; Florey et al., *op. cit.*, note 3 above.

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the “important role that it might have in the control of infections of war wounds”.<sup>7</sup> His use of crude filtrates predated those by other workers in the war.<sup>8</sup>

#### PENICILLIN IN THE MIDDLE EAST

Pulvertaft wrote in his quarterly Report, ending September 1942: “6 In vitro tests of a number of new bacteriostatic and bacteriocidal agents were made . . . among which was penicillin.”<sup>9</sup> In his Report ending December 1942, he wrote: “2 First rate results on burns, early infected wounds and late suppurating wounds has [*sic*] been achieved by treatment with Penicillin and Succinyl Sulphathiazole in lanoline locally.”<sup>10</sup>

Maurois named Pulvertaft’s first treated case as a New Zealand officer,<sup>11</sup> this account appears to have been supplied by Pulvertaft himself. Baldry gave a shorter account,<sup>12</sup> almost certainly derived from Maurois. The officer must be Case 1, treated with sulphanilamide from 30 August to 1 September and started on penicillin on 16 October.<sup>13</sup> There had, however, been two previous uses of penicillin: Case 3, on 17 August, “used as a test of action on organisms”, and Case 2, on 21 September. Twelve cases were treated with penicillin—Cases 1–6 and 9–14, although Cases 8 and 9 were also given crude filtrate. Maurois and Baldry both wrote that there were 11 cases, with complete recovery of 10.<sup>14</sup> Pulvertaft’s paper showed that Case 2 died and that treatment of Case 3 was “discontinued as test” after a second dose on 18 September.<sup>15</sup> In the Comment section, he mentioned “several other cases”, and that two suffered relapses with return of the organisms.<sup>16</sup>

The results were therefore not as clear as previous writers reported. However, the importance of these cases rested with the dramatic improvements that resulted after treatment with sulphanilamides had been ineffective; the “first rate” results obtained with Case 1 perhaps led Pulvertaft to forget the previous less dramatic cases.

Another, less obvious factor has been forgotten in the euphoria. The dramatic use of purified penicillin by Florey in February 1942 and by Fleming in August 1942 had been by injection into the bloodstream, resulting in an immediate dilution in the blood and other fluids of about 1 in 10,000. Pulvertaft had a severely limited supply of penicillin and many battle casualties to treat. Standard treatment was by irrigation with saline to remove pus and then local application of sulpha drugs, the former a routine originating from Fleming’s experiments in World War I.<sup>16</sup> Pulvertaft

<sup>7</sup> H. W. Florey and H. Cairns (eds.) *Investigations of war wounds. Penicillin. A preliminary report to the War Office and the Medical Research Council. Investigations concerning the use of penicillin in war wounds*, the War Office AMD 7/90D/43, 1943. The author has a copy from an unknown source: it is not traceable at the Public Record Office.

<sup>8</sup> M. Wainwright, ‘The history of the therapeutic use of crude penicillin’, *Med. Hist.*, 1987, 31: 41–56.

<sup>9</sup> Quarterly Reports of the Central Pathological Laboratory, c/o 15 (Scottish) General Hospital, M.E.F. Public Record Office, Kew, File WO 222/1465.

<sup>10</sup> *Ibid.*

<sup>11</sup> Maurois, *op. cit.*, note 6 above.

<sup>12</sup> Baldry, *op. cit.*, note 6 above.

<sup>13</sup> Pulvertaft, ‘Local therapy’, *op. cit.*, note 5 above.

<sup>14</sup> Maurois, *op. cit.*, note 6 above, and Baldry, *op. cit.*, note 6 above.

<sup>15</sup> Pulvertaft, ‘Local therapy’, *op. cit.*, note 5 above.

<sup>16</sup> Maurois, *op. cit.*, note 6 above.

substituted penicillin for sulpha, locally, thus avoiding dilution in the whole body, and reducing elimination via the kidneys and toxicity of the preparation. He received three batches of penicillin: the first, sent July 1942, was from Oxford, and two later batches of ICI penicillin were sent in November 1942 and March 1943.<sup>17</sup>

#### THE USE OF PENICILLIN

The following treatments were used from August 1942 to early January 1943:<sup>18</sup>

1. irrigation with a small volume of penicillin solution by catheter into a local sinus in the thigh: Cases 1–4, 6, and 10, and, into the thenar space in the hand, Case 11.
2. solid penicillin on the wound: Cases 2, 4, and probably 6.
3. penicillin spray: Cases 5, 6, 10–12, and probably 14.
4. gauze soaked in normal strength penicillin every 24 hr: Case 13.

The penicillin inhibited *Staphylococcus* at a dilution of 1 in 1,000,000 or more,<sup>19</sup> so there must have been very high concentrations of penicillin in the wounds for quite long periods.

Pulvertaft must have been very impressed with these results because he “wrote to Professor Florey asking him for a sample of his particular penicillium [*sic*]. From this he grew thick layers of the mould floating on endless gallons of broth in countless pails and tanks.”<sup>20</sup>

In his Report ending March 1943,<sup>21</sup> Pulvertaft wrote:

During the period under review further investigations have been made into the production and therapeutic efficiency of Penicillin. Sufficient cases have been treated to satisfy investigators as to the complete harmlessness and usefulness of the product. If applied to wounds infected with gram [*sic*] positive cocci or bacilli, removal of these organisms is almost invariably established within 24 hours, and the clinical progress of the wound is accelerated. Gram negative flora is [*sic*] not affected, but progress is not interrupted by their presence.

The crude product [penicillin broth] has proved satisfactory in wound treatment and harmless to animals. It is hoped to encourage its use in plastic surgery and prophylaxis of wounds.

#### USE OF PENICILLIN FILTRATES

In the 18 September 1943 issue of *Lancet*, Pulvertaft<sup>22</sup> detailed his experience with penicillin. The summary stated that the 15 patients were treated with two batches of penicillin described as “Florey” although the second batch of the calcium salt was from ICI.<sup>23</sup> Moreover, four cases were treated with culture filtrates: Case 9, (March 20 and daily until March 26), “Gauze and *P. notatum* filtrate”; Case 15, (April 16 and daily until April 25), “*P. notatum* culture filtrates, 10 c. cm. injected into cavity for two hr. daily before water drainage”; Case 7, (April 16 and daily until April 27),

<sup>17</sup> Florey and Cairns, op. cit., note 7 above.

<sup>18</sup> Pulvertaft, ‘Local therapy’, op. cit., note 5 above.

<sup>19</sup> Ibid.

<sup>20</sup> Morgan, op. cit., note 4 above.

<sup>21</sup> Public Record Office, op. cit., note 9 above.

<sup>22</sup> Pulvertaft, ‘Local therapy’, op. cit., note 5 above.

<sup>23</sup> Florey and Cairns, op. cit., note 7 above.

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“gauze soaked in crude penicillin”; Case 8, (April 20 and daily until April 26), “penicillin 1% in cavity and *P. notatum* filtrate gauze.”

Only Cases 7 and 15 were started on penicillin filtrate: the others had received British penicillin and Pulvertaft was clearly experimenting with different combinations of treatment. Only Case 15 was treated entirely with the filtrate. Case 8 was started with British penicillin (probably ICI from the date) on 7 April and then in combination with the filtrate. Details of the bacteria seen in smears and grown in culture were given for each day of treatment. Except in the four pages of case notes, there was no mention in the text of the locally produced penicillin. However, the last sentence of the Summary reads: “A few experiments with *Penicillium notatum* filtrates, made locally, gave satisfactory results.”<sup>24</sup> Details of the local production (and experiments ?) may have been removed by the editor, leaving only the summary.

Alan Morgan, then a pathologist with Pulvertaft and later a fellow professor at the Westminster Hospital, wrote that

The filtrate was applied locally to infected wounds by some of our surgeons, who found it to be very effective by the standards of the day, but apparently the venture was frowned upon by Florey and his team, who did not want their work on the extraction of pure penicillin to become confused by the unauthorised use of a crude brew. The result was that three pundits flew out from England to see what Pulvertaft was up to, but he put up a spirited defence of his procedure and the interview finished amicably. Soon, however, Florey’s penicillin became generally, if not abundantly, available in North Africa, making the crude substitute unnecessary.<sup>25</sup>

Norman Heatley, a member of the Oxford team, has written that “we all admired Pulvertaft’s activities”.<sup>26</sup>

In his Report ending March 1943, Pulvertaft gave the first details of production: “Production of crude Penicillin has proceeded, and much useful knowledge has been gained on the adjuvant action of light, potato extract and oxygen.”<sup>27</sup> Further details were given in the Report ending June 1943:

(A) A large number of experiments have been made, in an attempt to make crude Penicillin under M.E.F. [Middle East Forces] conditions.

As a result, a method of culture at pH. 5, filtration, and incorporation of 1 in one million merthiolate has been adopted. This product has a titre of 1 in 500, is stable for a fortnight at least, and contains enough merthiolate to prevent contamination.

The crude product, applied externally to infected wounds, appears to be just as efficient as the purified product.

It has been injected intravenously into a man in a dose of 200 cc without any reaction.

Production on a larger scale is now in progress, and a wider test is being applied.<sup>28</sup>

There was no further mention of penicillin production and use in later Reports.

<sup>24</sup> Pulvertaft, ‘Local therapy’, op. cit., note 5 above.

<sup>25</sup> Morgan, op. cit., note 4 above.

<sup>26</sup> Personal communication from N. G. Heatley.

<sup>27</sup> Public Record Office, op. cit., note 9 above.

<sup>28</sup> Ibid.

I have recently had the pleasure of meeting Professor Pulvertaft, who has added his memories to those of the records. He estimates that more than 10 gallons of filtrate were produced each week and that quantities were sent to other military hospitals and units as well as the Royal Navy and Royal Air Force. A RAF officer from a nearby hospital studied the production and, returning to his hospital, made and used the filtrate. The official Allied policy was that penicillin was a war product which should be kept from the enemy. Pulvertaft disagreed strongly with this attitude and when Turkish doctors came to see him, he gave them samples of *Penicillium* and told them how to make penicillin: they made it quite well.

Pulvertaft grew the mould on a sugar base which became acid. He added a sulphur-producing organism which made the medium alkaline and precipitated the penicillin. The supernatant was decanted and the precipitate was allowed to dry before use. Pulvertaft called the crystals Penamide and on his return to the UK tried unsuccessfully to persuade Burroughs Wellcome to manufacture it for sale in the UK. Some of this Penamide was improperly taken and sold on the black market when a member of the staff went on leave to the Levant. There is no record of Pulvertaft or Penamide in the archives of the period at the Wellcome Foundation.<sup>29</sup>

#### CONCLUSIONS

In the Official War History, Garrod wrote that the "treatment of battle casualties with penicillin was begun by Pulvertaft in Cairo, . . . as early as 1942 with very short supplies of locally prepared crude filtrate, and was later amplified by small supplies of penicillin released from the United Kingdom."<sup>30</sup> Garrod thus reversed the order in which Pulvertaft used penicillin.

Pulvertaft's work and his second paper were noted by Florey et al. in their *Antibiotics*, but not his work with filtrates.<sup>31</sup> Pulvertaft was not the only service doctor to make and use his own filtrate: the Royal Navy used it to treat gonorrhoea.<sup>32</sup> The filtrate was made at the Navy's Medical School in Somerset, but Reading has implied that this was in 1945–46.<sup>33</sup> However, Surgeon Commander C. A. Green, RNVR wrote to the Medical Director-General of the Navy (MDG) on 17 March 1943:

a start is being made therefore with the production of penicillin at the RN Medical School. This has been initiated on a small scale, making use of existing apparatus, but with the gaining of experience it is hoped to be able to increase production and finally to offer it for therapeutic purposes."<sup>34</sup>

On 12 April, Green wrote again and on 24 April the MDG asked Florey if Green could visit for a few days. On 28 April, Florey sent a very off-putting reply to Admiral

<sup>29</sup> Personal communication from Mrs M. F. Williamson, Assistant Archivist, The Wellcome Foundation Ltd., London.

<sup>30</sup> Garrod, *op. cit.*, note 6 above, p. 554.

<sup>31</sup> Florey et al., *op. cit.*, note 3 above.

<sup>32</sup> J. Howie, 'Gonorrhoea—a question of tactics', *Br. med. J.*, 1979, ii: 1631–2.

<sup>33</sup> C. A. Reading, 'Gonorrhoea—a question of tactics', *Br. med. J.*, 1980, i: 189.

<sup>34</sup> Production of penicillin at RN Medical School. Public Record Office, File ADM 1/15311.

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Griffiths, suggesting that industrial production was the most efficient and that small-scale production was very wasteful of time and resources. He was, however, willing to see Green.<sup>35</sup> These reasons were likely to have been behind his negative reactions to Pulvertaft's work. A long letter from Green to the MDG on 17 May contained only a short paragraph about penicillin production; this, the last letter in the file, suggests that the project went no further.<sup>36</sup>

We shall never know why Fleming did not persist with his penicillin broth for external use, but there must have been few suitable cases for treatment available at any one time.<sup>37</sup> He would have had to cultivate not only his penicillin but also many doctors in different clinics. Pulvertaft, on the other hand, had many battle casualties in the hospital and was already experimenting with local treatments. To prove the therapeutic value of the new drug, Florey had used all his penicillin on one patient. Pulvertaft, with a limited supply, chose not to use it all on one seriously ill patient, but rather on a number of patients, locally, as an adjunct to his experimental treatments.

Pulvertaft used his first Florey penicillin as an injection, very weak into the sinuses of the leg: then continued slowly with the other cases. What impressed him was the improvement produced by small quantities of locally-applied penicillin. With so many patients, it must have seemed worthwhile at least to try the crude filtrate. Although there would have been heavy demands on men and equipment, he would have been in a much better position than Fleming to begin production. Fleming's crude filtrates soon lost activity,<sup>38</sup> a problem which Pulvertaft seems to have overcome, perhaps because he added merthiolate and could use his filtrates quickly. There is no mention of the difficulties with contamination, production, etc. that hampered commercial manufacturers.<sup>39</sup>

It was surely much easier to see that crude penicillin filtrate might work when one knew that diluted, purified penicillin did. Pulvertaft and his staff and the medical officers of the Fifteenth (Scottish) General Hospital made a significant contribution, which was overtaken by the availability of purified penicillin. Pulvertaft's energy and acumen were recognized: "It is worth recording by the way, that both Buttle (from Italy) and Pulvertaft (from Cairo) were flown to Bizerta to advise Lord Moran and Brigadier Evan Bedford, the Consultant Physician MEF, during Churchill's startling attack of pneumonia in December 1943"<sup>40</sup>—but penicillin was not used on that occasion.

In World War I Pulvertaft was an infantryman in Palestine and later observer and fighter pilot in Egypt. After the war he qualified in medicine from Cambridge and went to Burma for a short time. He returned to medical appointments and was editor of *Discovery*. He contributed to newspapers including the *Manchester Guardian*. He returned to Egypt in 1940 and, later, Palestine. He came home in 1945 to the Westminster Hospital where he was made Professor of Clinical Pathology in 1946.

<sup>35</sup> Ibid.

<sup>36</sup> Ibid.

<sup>37</sup> R. Hare, 'Fifty years of penicillin', *Br. med. J.*, 1979, i: 1423.

<sup>38</sup> G. Lacken, *The story of penicillin*, London, Pilot Press, 1945.

<sup>39</sup> E. L. Smith, 'British penicillin production', *J. Soc. chem. Ind.*, 1946, 65: 308–14.

<sup>40</sup> Morgan, *op. cit.*, note 4 above.

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Several of his colleagues in the Middle East continued to work with him at the Westminster. He was a “brilliant and fluent teacher of Pathology”, with “versatility of performance and range of perception” combined with kindness. He wrote poetry and “over the cake for tea on a treponemal day one could hear more good ideas than most men have in a year”.<sup>41</sup> Professor Pulvertaft showed his gifts of perception, energy and persuasion in Cairo—“It is worth while being a doctor, these times,” he wrote, “but I shall be lucky indeed if I see again changes so significant and decisive as I watched those hot summer days.”<sup>42</sup> He did much more than watch.

<sup>41</sup> ‘Portrait. Professor R. J. V. Pulvertaft, O.B.E., M.D., F.R.C.P.’, *The Broad Way*, 1954–6, R 15: 106–8.

<sup>42</sup> R. J. V. Pulvertaft, ‘Reflections on fifty years of medicine’, *ibid.*, 1948–50, R 12: 167–70. Professor Pulvertaft, born 14 February 1897, died on 30 March 1990: for obituaries see the *Independent* (by J. R. Hobbs), 6 April 1990, and *The Times*, 11 April 1990.