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Penicillin: promise, problems and practice in wartime Edinburgh

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ABSTRACT While medical historians have paid ample attention to the introduction of antibiotics and their impact on hospital-based practice during and after the Second World War, the multiple issues surrounding their use in Scottish hospitals are sorely lacking in current discussions. Drawing on an extensive yet underused range of materials including patient treatment records, oral histories and medical correspondence, this paper explores the introduction of penicillin for civilian treatment at the Royal Infirmary of Edinburgh during the closing stages of the War. It highlights the success of the drug in clinical treatment as well as its shortcomings, offering an alternative view of its initial impact on surgical practice.

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INTRODUCTION

Medical historians have paid considerable attention to the introduction of penicillin during the Second World War and its revolutionary impact on surgical practice and systems for infection control in hospitals worldwide.[1,2] Scholars too have documented and debated the rising rate of wound infection and the emergence of antibiotic resistance as a global phenomenon during the post-war era.[3–5] Yet little has been said about the implications of antibiotic therapy for clinical practice in Scotland and, more generally, it is recognised that there is a dearth of historical knowledge of the clinical work undertaken in civilian hospitals during the Second World War.[6]

This paper seeks to redress these imbalances within the historiography by exploring the introduction of penicillin to the Royal Infirmary of Edinburgh (RIE) and examining its impact on the treatment of civilian patients during the closing stages of the War. This paper utilises a variety of hospital records including previously unused patient treatment records together with correspondence, minute books, oral histories and excerpts from the medical press. As in the treatment of war casualties, penicillin achieved great clinical results in civilian treatment at the hospital. However, the new therapy was shaped considerably and, in some respects, tainted by economic problems with regard to both the quantity and quality of supplies. Indeed, this paper will demonstrate that such considerations exerted a strong influence over the cases chosen for penicillin therapy, methods for administering the drug and, sometimes, clinical outcomes.

Complicating the traditional view that penicillin was perceived as a 'wonder drug' or even a 'miracle drug' when it was first introduced, this paper will also highlight the considerable and recognised threat posed by microbial resistance right from the beginning.[1,2]

MANAGING SUPPLIES: THE PENICILLIN COMMITTEE

Early in August 1944, discussions emerged regarding the dissemination of penicillin for civilian use in Scotland's hospitals. Until this point, penicillin had been in use at the RIE for just a few months. It remained under tight control and was reserved for the treatment of war casualties and for the purposes of clinical trials.[7] However, in early August 1944, the Deans of the four Scottish medical schools of the Universities of Edinburgh, Aberdeen, Glasgow and St Andrews (in Dundee) met with officials from the Department of Health for Scotland (DoHS) to arrange for its incorporation into civilian treatment.[8] The DoHS explained that the Ministry of Supply was providing some 120 million units (120 'mega' units) for the treatment of civilians in Scotland in August 1944. It was agreed that this sum would be distributed to the four schools as follows: Glasgow, 60 mega units; Edinburgh, 35 mega units; Aberdeen, 15 mega units; and Dundee, 10 mega units. At the request of the DoHS, each Dean established and led regional penicillin 'committees' through which supplies and priorities for use were determined at a regional level.[8] That it was envisaged that the Deans of the four university medical schools would play such a crucial role in incorporating penicillin into the Scottish healthcare system is indicative of the supremacy of academic medicine in Scotland and its pre-eminence over extra-mural teaching before 1948.[9] The remit of the new Edinburgh committee was to distribute the drug to hospitals across the South-Eastern Defence District, an area probably covering

Lothian and the Scottish Borders.[8] Its membership comprised: Professor Sydney A Smith, Dean of the University's Medical School; WG Clark, Medical Officer of Health for Edinburgh; TJ Mackie, Professor of Bacteriology at Edinburgh University and Bacteriologist to the RIE; and JR Learmonth, Professor of Surgery and Surgeon to the RIE.[7,10,11]

Despite the fact that penicillin was still a relatively new technology, the Edinburgh team already possessed considerable knowledge of how to handle, use and even produce the drug. Mackie's bacteriological team at Edinburgh University had been growing small amounts of penicillin for clinical use at the RIE since mid-1942.[12,13] By September 1943, however, the net yield amounted to only one mega unit, enough to treat just one patient.[12] This is indicative of the difficulties faced in British university laboratories in producing ample quantities of penicillin before the US method of mass production by deep-tank fermentation was adopted in 1945.[2] Learmonth, in collaboration with another bacteriologist, JP Duguid, had recently conducted an investigation into the drug's efficacy in treating war wounds inflicted during the D-Day landings of June 1944.[14] Under the new arrangements, from August of that year, penicillin supplies were kept in Mackie's University department before being distributed to hospitals across the region. These hospitals included not only the RIE itself but also the City Hospital for Infectious Diseases, Bangour Hospital, the Western General Hospital, the Royal Hospital for Sick Children, Leith Hospital and the Princess Margaret Rose Hospital. In that first month, the RIE obtained the largest share of the supplies reserved for civilian use in these hospitals, receiving eight out of 35 mega units.[15–17] The total share for civilian treatment in all hospitals increased to 50 mega units in January 1945 and 75 mega units in the following month.[18,19] Despite these increases, demand continued to considerably outweigh supply. This may explain why, for a brief period in early 1945, the Penicillin Committee considered issuing 'sub-standard' penicillin (defined as penicillin of a potency lower than 150 units per milligram) to its hospitals for topical use. These plans were soon abandoned.[20,21]

Awareness of the need to ration penicillin became widely apparent in October 1944, when the Edinburgh Penicillin Committee circulated a recent Ministry of Health memorandum entitled 'Recommendations on the treatment of civilian patients with penicillin' to all hospitals under its authority.[15,22] Indeed, the opening line of this publication stressed the need for economy in using penicillin and the remainder of its contents provide an insight into the ways in which the drug was rationed when it was first incorporated into civilian treatment in Edinburgh and elsewhere in the UK. Advising that all penicillin should be administered in hospital, the memorandum noted the following conditions as 'suitable' for treatment: staphylococcal infections (such as septicaemia, acute osteomyelitis and severe carbuncles); haemolytic streptococcal, pneumococcal and meningococcal infections (especially those resistant to sulphonamide treatment); and gas gangrene. Several conditions merited 'special consideration' when supplies allowed for it, such as eye infections; sepsis in burns and wounds; sulphonamide-resistant gonorrhoea; traumatic lesions (for example, compound fractures and thoracic injuries); complications associated with tuberculosis (such as acute empyema); and skin infections resistant to other forms of treatment. The Ministry of Health granted the local penicillin committees the authority to use penicillin on conditions other than those highlighted in the memorandum, again providing supplies were sufficient.[22]

The Ministry of Health advised against the use of penicillin to treat conditions caused by organisms which were not at that time known to be susceptible to the drug (such as intestinal infections and ulcerative colitis), while also excluding bacterial endocarditis and syphilis.[22] The inclusion of ulcerative colitis on the list of conditions inappropriate for treatment highlights the 'vexed question' that was the aetiology of this condition during the interwar period.[23] Indeed, the medical literature of the pre-penicillin period was awash with narratives about the infectious nature of the condition, with *Bacillus dysenteriae* highlighted as a potential cause.[24–26] Likewise, while penicillin would eventually revolutionise the treatment of syphilis, during the War there was a delay in introducing the new treatment as the full extent of its activity against the causative organism in the condition remained unknown.[27] This allowed one British clinician to state in January 1945 that Paul Ehrlich's discovery of Salvarsan in 1907 remained to that day the 'greatest advance in the treatment of [syphilis]'.[28]

The memorandum also provided advice regarding how to administer the drug both locally and systemically, often recommending the size and frequency of dosages. For example, for burns and deep wounds they encouraged the local application of a penicillin cream. For abscesses, they recommended a solution containing sterile water and at least 250 units of penicillin per cubic centimetre. In the treatment of dry wounds, they endorsed the use of a mixed sulphonamide-penicillin powder, blown directly on to wounds using an insufflator.[22] In 1945, Learmonth, surgeon to the RIE and member of the Edinburgh Penicillin Committee, touted the use of an insufflator as being the most economic method of applying penicillin powders in that they produced an even 'frosting' over the area to be treated.[29]

Such specific guidelines regarding where and when penicillin should be used and in what ways were bound up with issues of economy. Of chief concern to the Ministry of Health was the need to implement economy with penicillin by using it sensibly and minimising

wastage, owing to the scarcity of supplies and widespread demand. These problems, they envisaged, could be counteracted by developing and spreading knowledge of the properties and best uses of the drug.[22] James Whorton has documented the development of 'therapeutic rationalism' in the USA during the 20th century, which he defined as the 'conservative and informed use of drugs only in situations where the likely benefits significantly outweigh the risks'.[30] He writes that these risks, particularly where antibiotics are concerned, include toxicity, side effects and resistance.[30] Building on this, Scott Podolsky maintains that by the 1960s, and in light of the escalating cost of prescription medications in the USA, notions of 'rational' drug prescribing – particularly antibiotic prescribing – were now underpinned by issues of economy.[31] However, in British hospitals, antibiotics were closely linked to issues of economy right from the beginning, not because of the cost of the new therapy but because of the huge imbalance between supply and demand. The story of penicillin in British hospitals was therefore centred as much on ideas of economic rationalism as it was on therapeutic rationalism.

PENICILLIN TREATMENT AT THE ROYAL INFIRMARY OF EDINBURGH

To keep a watchful eye on penicillin consumption in Edinburgh, the local Penicillin Committee requested that clinicians kept records of the cases treated with penicillin and the amount of the drug used in each case.[15] Fifty-three of these treatment records from the RIE are held at the Lothian Health Services Archive, and dated between October 1944 and February 1945. Forty-six patients in the series were admitted as inpatients and the remaining seven were outpatients. The records contain information on the name, age and condition of each patient. They also cite dates of admission and discharge, the duration, method and dose of penicillin treatment and the results of treatment.[32] Their contents give an illuminating insight into the types of patients that were chosen to be among the first civilian beneficiaries of penicillin in British hospitals, while their meticulous detail demonstrates how the Ministry of Health's overarching aim of implementing economy operated at the individual patient level.

An indication of the age of the patients was given in 47 cases. The majority (29) were patients under the age of 30. From the 45 records giving specific ages, an average age of 31.5 years is noted.[32] The relatively young age of this group is perhaps surprising considering the predisposition of the elderly to infection and the age-associated decline of the immune system.[33] Arguably, the decision to treat the infectious ailments of these relatively young patients reflected the need to minimise wastage by giving penicillin to those with a better chance of recovery.

TABLE 1 Conditions treated with penicillin at the Royal Infirmary of Edinburgh, 1944–5. (Adapted from: LHSA. RIE penicillin treatment records, 1944–5. GD1/74/8/5. Note: 8 patients were recorded under two separate categories, hence the total of 61 patients).

Condition(s)	No. of patients
Osteomyelitis	17
Septicaemia	6
Gonorrhoea	6
Puerperal/suppurative mastitis	5
Abscess/multiple abscesses	5
Laceration	3
Compound fracture	2
Septic arthritis	2
Varicose/necrotic ulcer	2
Carbuncle, empyema, epithelioma, gangrene, gonococcal iritis, gunshot wound, haemothorax, pneumonia, pyaemia, septic burn, septic thumb, tendon sheath infection, ulcerative colitis	1 (for each condition)
Total	**61**

Table 1 shows that the ailments treated with penicillin at the RIE during this period were almost identical to those that the Ministry of Health had awarded priority status to. Osteomyelitis represented the most common condition in this series, as found in 17 patients.[32] This is perhaps unsurprising given the very successful results of a clinical trial of penicillin in osteomyelitis which was conducted at the RIE only a matter of months previously, using penicillin obtained from US pharmaceutical company Pfizer.[12] In that study, a mortality rate of just 2.5% was demonstrated in 40 patients despite a 50% incidence of staphylococcal septicaemia. In osteomyelitis, penicillin represented a considerable advance over sulphonamides which studies indicated had an associated mortality rate of 10%.[34] Only in one instance – the case of ulcerative colitis – was penicillin used against the Ministry of Health's wishes.[22,32] The broad range of conditions represented in Table 1 highlights not only that the Ministry of Health's guidelines for rational use were followed closely in Edinburgh, but also the degree of flexibility afforded to regional penicillin committees in deciphering who else could be selected for therapy. That Edinburgh's Committee chose a case of epithelioma for treatment is an interesting observation and likely reflects the longstanding association of cancerous conditions with bacterial infection.[35]

The exact quantity of penicillin used in this series amounted to 44,239,000 units. This sum represents 81.2% of the total amount used at the hospital during the period from October 1944 to February 1945 (54,500,000 units). It gives an average of 834,698 units

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per case, although the total individual amounts given ranged from 40,000 units to 4,200,000 units. Typically, patients at the higher end of this scale received penicillin by infusion. The infusion method involved administering, by drip, large volumes of penicillin continuously and over several days, thereby maintaining serum bacteriostasis at a satisfactory level at all times.[32,36] Length of treatment was calculated for all patients in the series and gave an average length of 9.2 days per patient. Methods of administration were recorded in 51 of 53 cases. The majority of patients (32) were treated via intramuscular infusion. This group comprised cases of osteomyelitis, pyaemia and septicaemia, among other conditions. Five patients with similar conditions received penicillin by intramedullary infusion. Eleven received intramuscular injections which were administered at regular intervals and typically over a relatively short period of time (usually less than 24 hours). From these 11, seven patients (all six cases of gonorrhoea and one of gonococcal iritis) were given penicillin dissolved in a mixture of beeswax and peanut oil or in a saline solution. The remaining ten patients, typically those with localised abscesses, received local treatment by injection. In many cases, penicillin was administered by two or more of the methods described here.[32]

Just months before the beginning of the period under analysis, a report of a combined clinico-bacteriological investigation into the therapeutic properties of penicillin, produced for the Medical Research Council, appeared in the *British Medical Journal*. In this report, a daily dose of 120,000 units over at least seven days was recommended in systemic administration.[37] The Ministry of Health recommended 100,000 to 120,000 units per day in cases requiring infusion and 120,000 units receiving intramuscular and/or subcutaneous injections.[22] The case notes did not always provide figures for total daily doses for each patient, although the administration of 100,000 units was relatively common in the 37 patients receiving penicillin by infusion. However, to some this figure represented the absolute bare minimum needed to treat infection and, to others, it fell far short of what was deemed necessary. Moreover, if the average total dose of penicillin given to each patient in this series amounted to 834,698 units and the average patient received 9.2 days of treatment, an average daily dose of 90,728 units per case per day can be deduced from these figures.[32] These doses were likely weakened further by the impurities that plagued wartime British-made penicillin. Indeed, the Ministry of Health noted that at that time, up to 60% of penicillin issued in powder or tablet form could contain impurities.[22] There is thus ample evidence to show that reduced-strength doses of penicillin were being administered at the RIE and probably elsewhere. It is widely recognised that this practice of giving sub-standard doses – also referred to as antibiotic 'underuse' – has significant implications for microbes and their capacity for resistance.[1] As will be demonstrated below, so too did it have implications for clinical outcomes in this series.

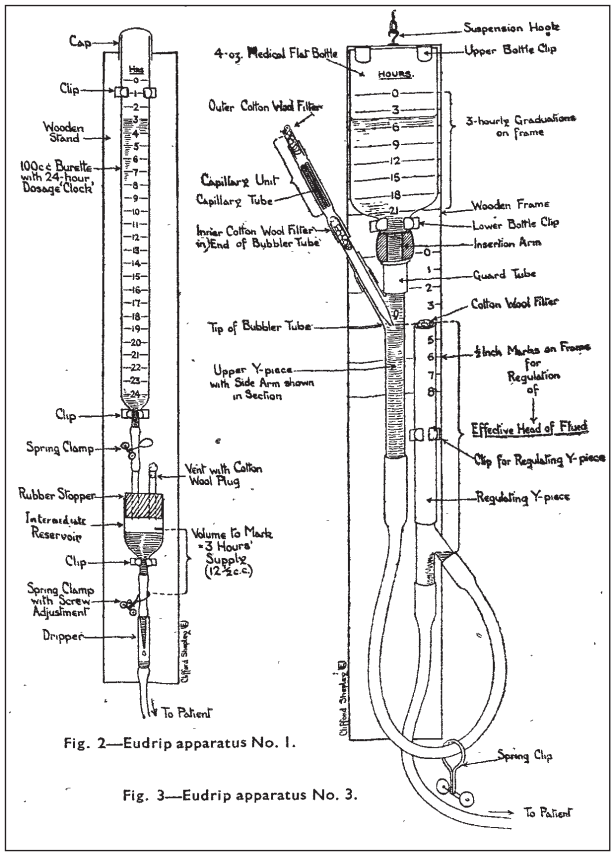

FIGURE 1 'Eudrip' apparatus for penicillin administration. Reprinted from [36] with permission from Elsevier.

The Eudrip apparatus (Figure 1) was used to administer penicillin by infusion. Devised in 1944 by the bacteriological and surgical staff of Edinburgh University and the RIE, this apparatus was available in two models ('No. 1' and 'No. 3').[36] The Ministry of Health gave detailed instructions for using both models in its memorandum on penicillin, suggesting that the Eudrip was used in hospitals across the UK during this period.[22]

To operate the Eudrip No. 3, the model which found favour at the RIE, the penicillin solution was stored in a four-ounce supply bottle before passing through a glass Y-piece, fitted into the neck of the bottle. This Y-piece also facilitated the inflow of air into the bottle which, in turn, determined the rate by which the solution passed through the apparatus to reach the patient. The rate of flow could be adjusted by raising or lowering the Y-piece.[36] One surgeon testified to the use of the Eudrip No. 3 when penicillin first appeared:

> …my recollection is that it was a simple glass medicine bottle in some cases, with a cork and a hole bore through it, and an almost home-made drip if you like, okay? And because, you probably know that the penicillin is very quickly excreted from the body, straight penicillin, and so the problem was to keep

> the blood level up….And if the patient was seriously ill, you had to keep the blood level high, and you could only do that by an infusion. So my first introduction of it was it being given in this improved drip-form, which was quite a novelty way of giving a drug at that time, by infusion.[38]

It was the nurse's duty to re-fill the supply bottle once daily and, after use, the apparatus was washed with distilled water before being autoclaved. The fact that the Eudrip No. 3 required relatively little attention from the nursing staff in order to carry out its function gave it an advantage over the No. 1.[36] Penny Starns has commented on the revolutionary impact of antibiotics on the nature of nursing work. She argues that penicillin undermined the traditional duty of care, hitherto regarded as a key component of nursing work. In her words, '[t]he days of administering hot poultices and sponge baths were over, and in some instances good old-fashioned nursing care was rendered superfluous'.[39] This change was also occurring in Edinburgh in connection with penicillin and particularly so with the introduction of the Eudrip. A nurse who trained at the RIE during the 1930s recalled the numerous practices (including administering poultices and providing fresh air) that were crucial to the nursing of infectious conditions 'without the aid of antibiotics'.[40] The arrival of penicillin therapy and the Eudrip apparatus, in minimising the nurse's role in the healing process, ultimately shifted the power to facilitate treatment from the nurse to the new technologies.

In this series, positive outcomes resulting from penicillin treatment were recorded in 48 cases (90.1%). The treatment forms indicated that the patient had improved notably and/or they had been discharged from hospital. Seven of these patients, most of whom were cases of gonorrhoea, were cured with penicillin having previously failed to respond to sulphonamide therapy. One patient with a tendon sheath infection was successfully treated with a sulphanilamide powder while receiving penicillin via intramuscular infusion. Before penicillin, tendon sheath infections, as one commentator noted in the *Lancet* in 1947, 'usually meant that the patient would be left with a stiff claw which he would gladly see amputated'.[41] The use of penicillin and sulphonamides together shows that in wartime Edinburgh, penicillin was deployed in what must be viewed as an early form of 'combination therapy' – therapy involving two or more antibiotics – which was popularised during the 1950s.[42,43] On at least four occasions, penicillin was given as a prophylactic measure: in one case, before a sequestrectomy; in another, before a leg amputation; in a case of haemothorax, where it was noted to have been used 'with great success' and resulted in the 'complete avoidance of infection'; and in a patient with severe lacerations to the hand which resulted in the 'avoidance of infection in what was an obviously heavily infected wound'.[32] Presumably the latter denotes a wound infested with bacteria but without any clinical symptoms of infection. Just three deaths appear in the series, giving a mortality rate of 5.7%. In all three instances, the records intimated that the penicillin was administered too late.[32]

Despite the overall successes achieved with the new treatment, ongoing issues with both the quantity and quality of penicillin were manifest in the patient records. These issues, as mentioned above, resulted in the use of impure, sub-therapeutic doses of penicillin which undoubtedly contributed to questions surrounding resistance. Indeed, the records provided concrete evidence of microbial resistance. On at least six occasions, some organisms – including those which are usually susceptible to penicillin – resisted treatment. In three of these cases, although it had no effect on the eventual clinical outcomes, treatment was stopped despite the lingering presence of bacteria. Three patients developed staphylococcal abscesses during or after treatment. One of these three records noted a 'poor result' in treating the abscess.[32]

These findings allow us to redefine the timeframe which historians traditionally use for the phenomenon of antibiotic resistance. Granted, as scholars traditionally assert, microbial resistance did not rise to prominence as a global threat until the 1950s.[3–5] Yet, there was a notable degree of resistance to antibiotics right from the beginning. Laboratory investigations conducted in Oxford as early as 1940 demonstrated the capacity for some bacterial strains to resist penicillin in vitro.[44] These case notes, however, served as an early indication that the phenomenon of resistance was entering the clinical sphere in Edinburgh. As early as April 1944, shortly before the period under analysis, experts advocated the routine bacteriological testing of infective cases to establish the cause of infection as a means of determining the efficacy of penicillin therapy in individual cases.[37] Evidence suggests that at the RIE, sensitivity testing was first performed in the wake of the D-Day landings in June of that year. It is known that Learmonth and Duguid conducted in vitro analyses of swabs taken from wounded soldiers arriving from Normandy to establish the sensitivity of infecting strains to penicillin.[14] One nurse who worked under Learmonth during the War testified to the benefits of penicillin in wound care but also to the need for routine testing at that time:

> Yes, [penicillin] made a tremendous difference. But there again, I can remember Sir James Learmonth saying so definite when penicillin came out, 'Now let's hope these never become too common'. You see, we always took a small [sample] of whatever was causing illness or blood or what have you, urine sample and made sure that the organism was sensitive to whatever we were giving. And his theory was that if that wasn't done routinely that the organisms would become insensitive to the…And this has happened

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> of course, [penicillin is] given out right left and centre.[45]

These early warning signs of resistance – manifest as they were both clinically and bacteriologically – are somewhat at odds with some historical perspectives on the theory of iatrogenesis: that is, that disease is often derived from clinical treatment itself.[46] Iatrogenic theories often portray physicians as wrong-doers and have considerably influenced some historians such as Richard Taylor and Ivan Illich.[47,48] Taylor, for example, contends that the phenomenon of antibiotic resistance resulted from widespread antibiotic use.[47] Issues of microbial resistance in Edinburgh at this early stage, however, were not the result of antibiotic overuse. That resistance issues featured so early in the penicillin story despite the strict controls imposed on its use at that time shows that, if anything, microbial resistance initially stemmed from underuse. But this was necessitated by economic circumstance and was out of clinicians' control. We must also remember the natural ability of bacteria to resist antibiotic treatment and consider Bud's argument that while poor antibiotic practice may certainly encourage resistance, nothing can be done to prevent natural bacterial evolution.[2,44]

A small number of cases highlight other issues surrounding the quality of penicillin in use at the RIE. Taylor ascribes the term 'second level iatrogenesis' to the experience of side-effects after clinical treatment with drugs, including antibiotics.[47] In this series, reactive inflammation around the site of the needle was recorded in two cases. In another case of acute gonorrhoea and prostatic abscess, penicillin was administered via intramuscular injection. It was noted that this patient's leg stiffened to the extent that he was 'almost crippled' for days after.[32] According to Bud, negative reactions to penicillin injections typically reflected the impurities contained within wartime penicillin. He noted that injecting penicillin in a suspension of beeswax and peanut oil – common at the RIE, particularly in treating gonorrhoea – was a popular wartime practice designed to counteract pain by reducing the number of injections that each patient was required to have.[2]

CONCLUSION

Supplies of penicillin for civilian treatment across Edinburgh grew slowly after August 1944. By February 1945, monthly supplies had risen from the initial allocation of 35 mega units to 75 mega units.[15,19] Over the next two months, the DoHS envisaged that the amount of penicillin used in Scottish hospitals would at least double, partly because a growing number of conditions (including syphilis) were now understood to be fit for penicillin treatment. The increasing use of penicillin required new systems for control and distribution. In February, the DoHS began the process of relieving Scotland's penicillin committees of their duties for control. In their place, specially designated 'distributing centres' were set up in hospitals to receive and distribute supplies. Owing to its considerable experience in using penicillin, the RIE became one such distributing centre and it played a major part in the dissemination of penicillin to hospitals in the local area. All duties regarding the drug's preparation and dispensing were assigned to its pharmacy.[49–51] As the Penicillin Committee's powers diminished and as the RIE's responsibility for penicillin grew, clinicians were no longer required to keep detailed records of the cases treated with the drug.[49] In the immediate post-war period, penicillin became available for use in Edinburgh in other forms with the arrival of penicillin lozenges, for example, in late 1945.[52] By May 1946, the RIE's supply of penicillin had grown to some 700 mega units per month, approximately 250 of which were reserved specifically for cases of venereal disease. As of 1 June of that year, the free issue of penicillin from the DoHS ceased. After this point, the RIE and other hospitals had to purchase penicillin through normal trade channels at a price (an estimated 15 shillings per mega unit) regulated by the Government.[53] Penicillin therapy looked set to continue to be bound up closely with issues of economy in post-war Edinburgh, with direct costs superseding problems with supply to become the leading concern.

In examining the new penicillin therapy as it emerged in Edinburgh during the closing stages of the Second World War, this paper provides some much-needed insight into the nature of wartime clinical and nursing work in civilian hospitals and into the early history of antibiotics and their implications for hospital-based practice in Scotland.[6] Traditional historical accounts of penicillin emphasise the euphoria generated by the drug when it was first introduced into the clinical sphere.[1,2] However, the findings outlined here offer an alternative view of the early history of penicillin. It has been shown that despite penicillin generating great clinical results during this period, its introduction into civilian treatment was complicated by economic difficulties and the necessity to use the drug rationally. This emphasis on rational use did not result from considerations of cost nor of side-effects – issues which did not come into play until the post-war period – but from ongoing issues surrounding both the quantity and quality of supplies.[30,31] These issues exerted a strong influence on the nature of the early penicillin therapy at the RIE. Although penicillin on the whole achieved excellent clinical results, these were counterbalanced to an extent by problems with supply. Undoubtedly, the scarcity and poor quality of wartime penicillin contributed to the phenomenon of resistance as it emerged within the clinical realm so soon after the drug was introduced.

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