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THE TREATMENT OF EARLY SYPHILIS IN THE ARMY.

BY

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[Chemistry of Penicillin.—... Of various formulae discussed from time to time the most likely one seems to be that known as the lactam formula, which is as follows:

\[
\begin{align*}
&\text{CH}_3, \\
&\text{CH}_3
\end{align*}
\]

\[
\begin{align*}
&\text{C} \quad \text{CH COOH} \\
&\text{CH}
\end{align*}
\]

The different penicillins so far examined seem to have the same general structure and to vary only in the nature of the side chain R. There is a difference in the nomenclature of the substances in Great Britain and the United States of America, as follows:

<table>
<thead>
<tr>
<th>R</th>
<th>British name</th>
<th>American name</th>
</tr>
</thead>
<tbody>
<tr>
<td>- CH_2CH_2CH_2CH_3</td>
<td>Penicillin I</td>
<td>Penicillin F</td>
</tr>
<tr>
<td>+ CH_3</td>
<td>Penicillin II</td>
<td>Penicillin G</td>
</tr>
<tr>
<td>- CH_2OH</td>
<td>Penicillin III</td>
<td>Penicillin X</td>
</tr>
<tr>
<td>+ CH_4CH_2CH_2CH_2CH_2CH_3</td>
<td>Penicillin K</td>
<td>Penicillin K</td>
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Penicillin I, with a pentenyl side chain, is the one produced by the original surface culture fermentation strains in England, whereas penicillin II is the one produced in the largest amount by more recent surface culture strains and by the submerged culture...
The discovery of penicillin has wrought great and sudden changes in the treatment of syphilis, but, as in previous such revolutions in the treatment of this disease, its end effects cannot be foreseen at this stage. In consequence, the treatment of syphilis is in a state of flux and doubtless will remain so for a few years to come. It is thought, therefore, that non-venereologist medical officers might be interested in a review of the situation affecting the British Army as it stands in July, 1946.

At the beginning of the war the standard treatment for all early syphilis in the Army was organized on a schedule consisting of four courses of arsenic and bismuth. Each course consisted of 5·85 grammes of neo-arsphenamine and 2·0 grammes of bismuth. A rest period of four weeks was given between courses and at the conclusion there was a surveillance period of two years, during which time the patient received repeated blood tests and a cerebrospinal fluid examination.

The main disadvantages of this mode of treatment were the length of time involved with the repeated attendances at hospital and the complications, such as jaundice and arsenical dermatitis. However, under Brigadier Osmond's wise leadership, the difficulties of administration were overcome and, considering the successive events of threatened invasion at home, continual air attacks and sending of vast armies overseas, when one examines the old 1,1247 cards, one is amazed at the very high proportion who satisfactorily finished their treatment.

As regards the complications, the incidence of jaundice was the most perplexing one. This complication had a peacetime incidence of less than 5 per cent and this remained so until the spring of 1941, when it rose steadily, and by 1943 over 50 per cent of cases treated in some clinics suffered from this complication [1]. The jaundice was often severe and necessitated the patient being immobilized in hospital for some weeks, and it was at first thought that this was due to the effect of the arsenic on the liver. Later attempts to reduce the incidence of the disease by the prophylactic oral administration of sulphur containing amino-acids proved unsuccessful [2].

Following the suggestions made by Dr. MacCullum [3] and Lieutenant-Colonel Bigger [4] the possibility that the jaundice might be caused by an infective virus passed from patient to patient during the administration of the injections was then explored. Up to this time it had been common practice in military and most civilian clinics to sterilize the syringes by boiling at the beginning of a session but only to use methylated spirit or other disinfectants between injections for sterilization purposes. This theory was confirmed by Lieutenant-Colonel King et al. [5] working at Netley, and later by Major Laird at Preston [6] who, by adopting an operating theatre kind of technique in the giving of injections, were able to banish jaundice from their clinics.
Sterilization of syringes by boiling between injections was soon made general for all hospitals. This has controlled the disease but has not altogether stamped it out, for occasional cases still occur, and, if the precaution of boiling were relaxed, doubtless the disease would break out anew. The introduction of boiling of syringes nearly coincided with the use of penicillin, so that there was a double change of technique, but, even allowing for this, the following graph is of interest, as it shows the striking change in the numbers of jaundice cases admitted to the Military Isolation Hospital, Harrow Road, from 1944-1945. It will be seen that the vast numbers of jaundice admissions drop almost to zero, while the number of syphilis admissions per month has actually increased over the same time. This is of added interest, as, after June, 1945, arsenic injections were renewed—this time in conjunction with penicillin. The odd case of jaundice, however, still does occur.

As the war progressed, as a result of work in the U.S.A. [7] it became evident that syphilis could be cured by a quicker if more dangerous means by an intensive form of arsenical treatment employing an arsenoxide ("Mapharsen") which was, and still is, much in vogue in the U.S.A. The dose of this drug is one-tenth of the corresponding dose of neoarsphenamine. This intensive treatment involved the giving of 1,200 mgm. of "Mapharsen" five or eight days by means of an intravenous drip. One-day treatments of arsenic combined with fever were also employed, but did not prove successful. As with other new treatments, this was found to have its complications attendant on the treatment given quite apart from the therapeutic results obtained.
The Treatment of Early Syphilis in the Army

this case the main worry was that of arsenical encephalopathy. This complication, manifest by headache, pyrexia, drowsiness and sometimes coma and death, was only seen very rarely under the older long term regimes, though it had a much higher incidence in Indian troops.

Arsenical encephalopathy was rendered much less alarming by the arrival of B.A.L. This preparation (British Anti-Lewisite), which was developed in connexion with chemical warfare as an antidote against organic arsenicals, has the property of being able to remove the arsenic from combination with the cells and enables it to be excreted as a relatively non-toxic substance. It has been found to be of value if given early in encephalopathy, dermatitis, and agranulocytosis when due to organic arsenical substances.

The possibility of this grave complication was one of the reasons why this treatment was not pursued in the Army as a general measure, though several preliminary trials were made in different centres with a modified intensive schedule on a twenty-day basis giving 1,200 mgm. of “Mapharsen” in twenty daily injections with the addition of bismuth.

The continuance of these schedules of intensive arsenical treatment instituted solely for the purpose of shortening the treatment was rendered unnecessary with the introduction of penicillin. This was first given for syphilis by Mahoney et al. in 1943 [8] who, as a result of animal experiments, chose a dose of 1-2 million units and had success in four cases. So inspired was the calculation of the dose thought to be that most of the early schedules used in America employed this dose over varying periods of time. When the drug came to be applied to the Services, the dose was doubled and 2·4 million units given in three-hourly night and day injections of 40,000 units each (for seven and a half days). This was later copied by the British.

The immediate results were remarkable for at last there was an intensive form of treatment without any serious risks and the intensive and the long term arsenic schedules were discontinued and all syphilis in the Army was treated on this regime. Early in 1945 the Central Syphilis Register was opened and so there was a method of checking the relative efficiency of different treatments. Soon after this the European war terminated and demobilization began, and, as syphilis has to be followed for at least two years for convincing results and for life for conclusive ones, it was realized that even the Register could not give the ultimate information, though it might provide some very interesting interim data, and indeed was, perhaps, the only machine in the country which could do so.

As the months progressed, it became evident that all was not well, for a comparative rarity of the earlier treatments—the mucocutaneous relapse—was making itself felt in the clinical field. Sores were relapsing and condylomatous or moist papular lesions were reappearing in the genital area containing motile Spirochaeta pallida and associated usually with a relapse in the serological titre of the blood. The relapses, therefore, were of an infectious type and their apparent increasing frequency gave much food for thought.

An analysis was made at the Central Syphilis Register and some 270 cards were selected where the patients had been followed for six months or more on
both the 2·4 million units of penicillin schedule and the twenty-day intensive arsenic and bismuth scheme. Disappointment has been expressed in some quarters that this series was not larger, but it has to be remembered that the Register had only been in full operation for some months (and six of these were required for the follow-up) and, added to this also, demobilization had commenced. The percentage of failures was found later to coincide with the American figures, not available at this time, and showed a failure rate at six months of 8 per cent on the penicillin schedule and 2 per cent on the twenty-day regime [9].

As a result of this, it was decided that 2·4 million units alone was not enough for the treatment of early syphilis. Eagle had shown experimentally [10] that penicillin and arsenic had a synergistic action in the treatment of rabbit syphilis, and Lieutenant-Colonel Marshall conferred with Dr. Selbie to see what doses of arsenic could reasonably be combined with penicillin in the treatment of the disease in man. A general experiment in Home Commands was then started. The Military Hospitals at Netley, Knaphill, Catterick, and Harrow Road employed a regime consisting of 2·4 million units of penicillin combined with ten daily injections of 0·06 grammes "Mapharsen." The remainder, with the exception of the Military Hospital at Chester, used penicillin only, but the dose was increased to 4 million units. Chester continued with a schedule, which was in use at Preston prior to the commencement of the experiment, consisting of 2·4 million units of penicillin, plus 400 mgm of "Mapharsen," plus 2·0 grammes of bismuth. To date, some 1,000 cases have been treated by the combined penicillin and arsenic schedule, some 600 with penicillin only and about 800 with the combination of three drugs at Preston and Chester. Complications with the combined arsenical and penicillin regime have been relatively small though there have been two instances of encephalitis, both of which recovered and both of which received B.A.L. It was intended to treat 1,000 cases by these regimes before assessing results. It is obvious that to obtain a failure-rate figure for six months will require a few more months yet.

Owing to demobilization, it is impossible to say how this experiment is going. Apparently from reports received the schedule of four million units only has produced the least number of known failures, but, as this regime is used in the smaller clinics, the individual experience of relapses would be smaller. At the Military Isolation Hospital, Harrow Road, some 550-600 cases have been treated and I personally have seen 9 relapses occurring in periods up to eight months. As only about one-fifth have attended the hospital after six months, it is impossible to state whether this is good or bad, though it does not appear very encouraging. Nearly as many failures, too, have been found in the Chester series.

In February of this year the United States held a large meeting in Washington under the auspices of the United States Public Health Service and the National Research Council. I was privileged to attend as an observer. Here the combined work of some 43 clinics who had participated in a research study of the effects of penicillin in syphilis was presented. The data offered at this
meeting [11] showed that the relapse rate on the 2.4 million unit schedule was 15 per cent in eleven months, though it was shown that the addition of arsenic and bismuth to a penicillin schedule lessened the liability to relapse. Non-penicillin schedules produced better results in the same period: the five and the eight days intravenous drip showing an 8 per cent relapse and the more prolonged Eagle twelve weeks system where “Mapharsen” was given three times a week and bismuth once a week over twelve weeks produced a relapse rate of only 3.5 per cent.

Meanwhile venereologists in Britain while having none of the vast American organization to guide them were forming similar conclusions for themselves and civilian clinics generally were combining penicillin with both arsenic and bismuth. The field was still further complicated by the arrival of penicillin in oil-wax preparations which cause a delay in the absorption and excretion of the drug so that the daily dose may be given in one instead of repeated injections. This tended to cause the penicillin doses to be increased somewhat for reasons of safety.

As a result of all this, it was decided that the Army at home should continue the experiment that has been started until the analysed data could be obtained. All these schedules it will be remembered contain treatment well above the bare 2.4 million units of penicillin. Overseas Commands on the other hand have been recommended 2.4 million units of penicillin plus one course of neoarsphenamine old style. This it will be observed is a departure from the intensive principle of recent years and is the first step on the road back to pre-war treatment: whether this is to be the only step or the first of several remains to be seen.

Recently has come to light a matter which alarming in its immediate prospects may ultimately prove a timely revelation that may once again restore penicillin to its position of two years ago. It has been reported from America [12] that within a week of the Washington meeting some disturbing information had been obtained. This was that two laboratories working on the effects of penicillin K on rabbit syphilis had found that this fraction was notably less effective than penicillin G. Following this, one centre reported a paradoxical result in so far as a schedule of 1.2 million units over three and three-quarter days was found to be more effective than one at a later date with double the dose over double the time. As it was known that commercial penicillins of recent years have contained an ever-increasing amount of penicillin K, this prompted a further large-scale analysis of results in respect of the time factor. It was then evident that cases treated before May, 1944, did markedly better than those treated after that date. It was concluded that certain commercial penicillins processed in recent months are less efficacious in the treatment of syphilis than were the preparations available two years ago. It is probable that some of the decreased therapeutic effect is due to the increased amount of penicillin K which has been present in the commercial preparations of many manufacturers. The existence of other factors such as the removal of possible therapeutically active impurities must also be considered.
The response to this sudden and unexpected bombshell has been very rapid. Steps were at once taken in America by all manufacturers to reduce the K content of commercial penicillin and practically all the commercial penicillins available now consist predominantly of G. One manufacturer indeed has already placed on the market a crystalline product of G containing at least 95 per cent of G, and new research schedules in the U.S.A. are employing crystalline penicillin G in schedules of 2.4 and 4.8 million units over seven and a half days as from July, 1946 [13].

And so the difficulties seem to have been overcome almost as soon as they arose, and the research continues with increased vigour.

Meanwhile, in this country at the time of writing, venereologists are so divided in their opinions as to the correct method how penicillin should be administered that it is to the co-operative figures of the United States and, it is hoped, to the figures provided by the Central Syphilis Register that they must turn. Later, perhaps, venereologists in civilian life may be joined in groups either voluntarily, for there is nothing to stop them doing that now, or compulsorily, so that schedules can be tried and analysed on a scale comparable with American methods.

REFERENCES.