THE TOXIC EFFECTS OF TEN DAILY INJECTIONS OF
MAPHARSIDE COMBINED WITH PENICILLIN IN THE
TREATMENT OF EARLY SYPHILIS.

BY

Lieutenant-Colonel R. R. WILLCOX,
Royal Army Medical Corps.
Lately Advisor in Venereology to the War Office.

[Received March 16, 1947.]

In January, 1946, as the results of the treatment of early syphilis by means
of 2·4 million units of commercial penicillin over seven and a half days were
not as good as had been anticipated from first experiences, it was decided to
place the treatment of the Army at home on an experimental basis and to
increase the amounts of spirochætocidal substances given.

Approximately one-half of the patients were then treated with four million
units of commercial penicillin in aqueous solution administered in one hundred
three-hourly injections of 40,000 units. The remainder were given a com­
bined penicillin and arsenic schedule which, in its experimental trials using
neohalarsine or mapharside, had been found by Marshall to show promising
results [4]. This consisted of 2·4 million units of penicillin, given in sixty three­
hourly injections, with ten daily intravenous injections of 0·06 grm. mapharside.
This latter amount was thought, from previous experience in the intensive field,
unlikely to have the disadvantage of excessive toxicity and at the same time
to comprise a more efficient, but still rapid, treatment for early syphilis.

It was decided to treat 1,000 cases on each of these two schedules, while
another hospital employing 2·4 million units of penicillin, as before, plus
400 mg. of mapharside combined with one grm. of bismuth (a rapid treatment
schedule commenced by Major Laird) should continue. Before the end of the
year, over 1,000 cases had been treated by each of the three schedules and the
experiment was concluded. It was planned that the analysis of the results
would take place through the Central Syphilis Register at the War Office,
though it had been feared that there would be a big fall off in the follow-up as a
result of demobilization which was taking place on a grand scale. The work
in this respect could be considerably improved if civilian clinics respond to
the Ministry of Health letter asking for particulars of discharged Service men attending civilian clinics to be sent to the Service departments concerned [5].

Preliminary reports as to the results obtained in those patients successfully followed up at individual hospitals were not encouraging [10]. Partly for this reason, and partly owing to the disturbing information concerning the variants in the content of commercial penicillin with the relative ineffectiveness of penicillin K [8], the Army was placed on a safer, if longer, schedule of four million units of penicillin over ten days plus a full course of neoarsphenamine and bismuth over ten weeks. This schedule was also adopted by the R.A.F.

The object of this paper is to describe in broad measure the overall toxic effects obtained with the penicillin and mapharside regime and, in greater particular, those of 405 of a greater number of cases treated at one of the four hospitals concerned. The therapeutic results will not be discussed at any length as these will be forthcoming in due course in the final analysis of the experiment as a whole. However, as a modified intensive treatment with mapharside may yet play some part in the rapid treatment of early lues, a detailed report of the toxic effects encountered may prove of interest.

Mapharside (oxyphenarsone hydrochloride) is a drug which has been known for many years but only came into prominence immediately prior to the penicillin era when praiseworthy attempts were made in the U.S.A. to evolve a more rapid treatment for syphilis, attempts which, even with the enormous help derived from penicillin, have not yet achieved unqualified success. The main disadvantage of such intensive treatments with mapharside has been the increased incidence of what was formerly a rare event—the dangerous complication of arsenical encephalopathy. This complication is described severally as having, under prior long-term methods of treatment, an incidence of between 1:135,000 and 1:28,000 injections. When intensive methods came to be employed, it rose to 1:05 per cent of patients (as reported in the collected tables by Stokes [9], it being shown that the mortality was in inverse proportion to the period over which the drug was given. The incidence of encephalopathy though usually rare under the long term schedules, was found in World War II to have a high incidence in Indian troops, especially Tamils. Prebble [7] described 187 cases in India Command occurring between August, 1943, and March, 1945, all but two were Indian patients.

The dosages of mapharside employed in the intensive methods were, for example, 1,200 mg. by intravenous drip over five days; a similar dose over eight days and also 1-75 mg. per kilo in a single day. Multiple injection techniques were also employed giving 1,200 mg. of mapharside over longer periods of time. The United States Forces in Europe used a twenty-day scheme giving (combined with bismuth) 20 mg. per kilo body-weight in twenty equal daily doses and, on such a regime as this, the toxic effects of the drug were markedly less. Pillsbury et al. reported over 3,000 cases treated with no mortality [6].

Apart from the extensive American literature, there have been several recorded British experiences. Lydon [2] reported 5 cases of encephalopathy in 53 patients treated with 750 mg. of mapharside given in five two-hourly injections of 0-03 grm. daily for five days. Lloyd Jones and Maitland [1] reported...
three instances of encephalopathy in 241 cases of early syphilis treated by daily injections of 0.04 to 0.06 grm. of mapharside given for ten, twenty or thirty days depending on the duration of the syphilis. On the other hand, Macfarlane [3] treated 73 cases with 0.06 grm. of mapharside daily for twenty days, 19 with the same dose daily for thirty days and 28 with the same dose three times weekly for seven weeks and there was no case of encephalitis and the mortality was nil.

**The Schedule.**

The course was intended only for cases of primary or secondary syphilis and consisted of 40,000 units of commercial penicillin given three-hourly to a total of 2.4 million units combined with ten daily injections of 0.06 grm. of mapharside commencing on the second day, though, in those cases where the primary fever had been severe and had not resolved by this time, the latter was postponed until the temperature was normal. The patients were kept in hospital but not always in bed and routine white cell counts were performed on the first or second day, the fourth to fifth and the eighth to ninth day. The urine was tested daily for urobilinogen and albumen, though jaundice and kidney complications were absent in this series. The patients themselves were examined daily for toxic-dermal reactions and a four-hourly temperature record was kept.

**The Hospitals.**

This regime was employed at four hospitals. Three of these had facilities for good nursing while one had not. The writer was working at the last and, as a result of this, the more minor complications, which also arose at the other hospitals, received perhaps a little more respect than they deserved as far as modifying treatment was concerned. In all it was the practice, when any arsenical complication occurred, to discontinue the mapharside and extend the penicillin course to four million units.

The experience of serious reactions was, on the whole, small. There were three marked (one fatal), one mild and one doubtful case of encephalopathy in over 1,340 cases treated. This represents an incidence of 1:266 and a fatality rate of 1:1,340.

*Hospital A.*—Out of 219 cases treated only 10 showed secondary fever.

*Hospital B.*—Some 310 cases were treated and up to the last minute there were no untoward reactions apart from 2 cases of marked ninth-day erythema and one of urticaria. The former was treated with B.A.L.¹ though it was not certain that this drug accelerated recovery. The penultimate case showed secondary fever which was treated with B.A.L.; unfortunately followed by unexpected death in which the post-mortem findings were minimal but were attributed to arsenical encephalopathy.

*Hospital C.*—Of 243 cases treated, an interruption was made in respect of 22. 14 of these were for secondary fever, 6 for dermatological reasons (mainly urticaria and possibly due to penicillin), 1 for leucopenia and 1 for encephalopathy.

British Anti-Lewesite—2, 3-Dimercaptopropinol.
The latter case was one of latent lues and the encephalopathy was heralded by an epileptiform convulsion, following quickly on the eighth injection, and coma soon ensued. During the next three days some 21 c.c. of B.A.L. were administered and the patient recovered.

Hospital D. — Some 570 patients were treated on this or similar schedules. There was one established, one mild and one doubtful case of encephalopathy. The severe case arose in a man with late secondary syphilis after only four arsenical injections had been given. He exhibited slight fever, headache, photophobia, extreme lethargy and inability to respond to the spoken voice or other external stimuli, associated with a markedly raised protein content of the cerebrospinal fluid. He was never unconscious and had no epileptiform seizures. He received B.A.L. and made a steady, if slow, recovery.

The mild case showed vomiting, a temperature of 99° F. and one epileptiform fit following immediately upon the tenth injection at the termination of treatment. He was given a short course of B.A.L. but was actually never really ill. The doubtful case had received seven injections when he complained of headache and had a temperature of 98·8° F. and also exhibited an epileptiform convulsion. Such fits, however, had occurred before the patient contracted syphilis. Apart from discontinuing the drug, no specific treatment was given.

There follows an analysis of 405 medically unselected patients treated on this regime. The remainder consists of some treated on similar but not identical schedules using neohalarsine, and others of the other Services treated concurrently on whom the data is not available in retrospect, though it is known that no serious complication occurred amongst them.

The Cases.

The patients were as follows:—

<table>
<thead>
<tr>
<th>Type of Syphilis</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seronegative primary</td>
<td>166</td>
<td>41·0</td>
</tr>
<tr>
<td>Seropositive primary</td>
<td>164</td>
<td>40·5</td>
</tr>
<tr>
<td>Secondary syphilis</td>
<td>75</td>
<td>18·5</td>
</tr>
<tr>
<td>Total</td>
<td>405</td>
<td>100</td>
</tr>
</tbody>
</table>

All were adult white males of an average age of 27·68 years. The average age of contraction was thus 1·6 years lower than that of 556 cases treated at the same hospital early in the war.

The Blood-Counts.

The white cell counts of these patients, both before and during treatment, have been described in another place [11]. The initial counts showed no startling distinctions between seronegative primary, seropositive primary and secondary syphilis. There was only a very minimal increase in the numbers of lymphocytes and perhaps the large mononuclears as the disease progressed. Under treatment there was nothing distinctive in the reactions of the white cell count according to the duration of the disease, though there was a general fall in the total count amounting to approximately 15 per cent. This decrease was most noticeable in respect of the neutrophil polymorphonuclears (19 per cent) though the large mononuclears and the lymphocytes, both showed a
drop of 8.5 per cent. The eosinophils remained about stationary and the
basophils showed a slight tendency to increase. Owing to the greater fall in
the polymorphonuclear neutrophils, there was a small relative increase of all
the other elements in the average percentage counts of the later examinations.
Cases showing a secondary pyrexia had a higher, those with severe Herx-
heimer reactions an average and those that later showed a leucopenia a lower
than average initial white cell count. A more than average drop was noted in
those showing dermatological complications and arsenical encephalopathy.

It was customary to modify treatment, suspending the arsenic and increasing
the penicillin to four million units, if the total count fell below 4,000 or the
neutrophil count below 40 per cent, though figures of below 5,000 and 50 per
cent were very suspect and were frequently acted upon.

14 of the 166 seronegative primaries, 8 of the 164 seropositive primaries and
8 of the 73 secondary cases had their treatment altered on this account. No real
instance of agranulocytosis or aplastic anæmia occurred and all the affected
blood-counts made a spontaneous and complete recovery.

HERXHEIMER REACTIONS.

Pyrexias in the first twenty-four hours of treatment of between 99 and 104° F.
were noted in 27 seronegative primaries, 30 seropositive primaries and 13 of the
secondary cases. There was thus no significant difference in the incidence of
this reaction according to the duration of the syphilis. There was nothing
significant either in the behaviour of the white cell counts in the treatment
of these cases and, apart from a short delay in commencing the administration
of arsenic, no modification was made in the schedule.

UBROBILINOGEN IN THE URINE.

There were no cases of toxic jaundice arising during, or shortly after, treat-
ment though two cases were seen of the so-called syringe-transmitted variety
with the usual hundred-day incubation period. However, 19 cases showed
urobilinogen in the urine while actually receiving arsenic. Nine occurred on one
of the first two days, being attributed to the pyrexial Herxheimer reaction.
Two cases arose on each day of treatment from the fourth to the ninth day inclu-
sive. Apart from an occasional temporary suspension of the mapharside for
one day no other modifications were made and the condition did not recur.

SECONDARY PYREXIA.

This implies a rise of temperature after the primary fever had completely
subsided or, if no such primary fever was observed, a rise of temperature forty-
eveteight hours or later after the onset of treatment. Fourteen (8.4 per cent) of the
seronegative primaries; 19 (11.6 per cent) of the seropositive primaries and 11
(14.6 per cent) of the secondary cases showed this complication. There was
thus an increasing incidence according to the duration of the disease.

The white cell counts of these cases showed a slightly higher initial-count
though the proportionate drop was almost identical with the average for the
whole. Of these 44 cases, in 20 the treatment with mapharside was resumed
Treatment of Early Syphilis

after a stoppage of one or two days; while in the other 24 it was discontinued for good. Of this latter group, 7 had more or less severe reactions and included the 1 severe, 1 mild and 1 doubtful case of arsenical encephalopathy which have already been described. There was also 1 case with severe headache, 1 with tightness in the chest and 2 with ninth-day erythema.

**DERMATOLOGICAL COMPLICATIONS.**

In addition to the 2 cases of ninth-day erythema with pyrexia, there were 2 other instances of this disorder. Two others suffered from urticaria and possibly the penicillin was to blame, while 3 others showed seborrhoeic types of reaction in which it was deemed wise to discontinue the mapharside. The majority of these cases occurred towards the end of the ten-day course and the white cell counts, while similar to the average for the whole in the initial count, fell to a much greater degree while under treatment, a finding which was also present in the 3 cases of actual or suspected encephalopathy.

**HEADACHE AND OTHER SYMPTOMS.**

Nine cases complained of headache without pyrexia, and treatment was stopped in 5. Treatment was also modified once for abdominal cramps, once for severe nausea, once for tinglings in the right forearm, once because of vomiting, once for a syncopal attack and in 1 patient who developed night sweats and was referred elsewhere for more detailed chest examinations.

Complications in which it was deemed necessary to modify treatment arose in 72. Thirty-two were in seronegative primaries (19·3 per cent), 21 were in seropositive primaries (12·8 per cent) and 19 in secondary cases, no less than 25·33 per cent. In the majority the modification consisted only of the omission of the last one, or possibly two, of the arsenical injections. If more than two were required to be withheld, extra penicillin was given raising the total to four million units.

**CLINICAL RESULTS.**

Little will be said at this stage as to the clinical results. Owing to demobilization and other factors, the individual hospitals suffered from a great run down in the follow-up, though it is hoped that information will be forthcoming concerning those cases transferred to other centres and from civilian clinics in response to the Ministry of Health letter and that finally some statistically satisfactory figures will be available. Only approximately 20 per cent of this series were seen during the one hundred and twenty to one hundred and eighty day period after treatment, and the month by month percentages of the seropositive cases reaching seronegativity were:

<table>
<thead>
<tr>
<th>Percentage Becoming Seronegative Month by Month.</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>nil</td>
<td>33·3</td>
<td>65</td>
<td>75</td>
<td>76·6</td>
<td>86·2</td>
<td>83·3</td>
<td></td>
</tr>
</tbody>
</table>

**THE FAILURES.**

Eighteen cases of relapse-reinfection were personally observed, 4 of which were seen at civilian hospitals and not as part of the reduced follow-up that
has been described. Of these cases, 4 arose from seronegative primaries, 11 from seropositive primaries and 3 from the smaller number of secondary cases. Of the 14 who were originally seropositive, 10 had become completely seronegative in the interval before the relapse-reinfecion while 4 had not.

Dark-field positive lesions were found in 13 of the failures, in 6 of which the lesions were multiple though not always of an obvious nature. One of these cases was associated with a syphilitic hepatitis, showing jaundice with an enlarged liver in addition to dark-field positive lesions on the scrotum. Dark-field positive lesions with a negative blood were noticed in 2. Serological relapses, in cases which previously had been completely seronegative, occurred in 4 and 1 case had seroresistance associated with a non-healed sore in which treponemata could not be recovered at six weeks.

Some of these cases were undoubtedly reinfections and the wives were known to have contracted the disease in the interval between the attacks in 3. The time between the original infection and the relapse-reinfecion varied between two and eleven months, average 4·4 months.

TIME INTERVAL BETWEEN ORIGINAL INFECTION AND RECURRENCE.

<table>
<thead>
<tr>
<th>Months</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

SUMMARY.

The toxic effects of a schedule consisting of 600 mgm. of mapharside given in ten daily injections combined with 2·4 million units of commercial penicillin have been described.

In all nearly 1,350 cases were treated and there was 1 fatality. In addition there were 2 severe, 1 mild and 1 doubtful case of arsenical encephalopathy. No immediate case of jaundice occurred in the entire series.

Four hundred and five of the cases treated at one hospital have been studied in greater detail.

Treatment was modified in 72 of which 30 were due to an excessive fall in the white cell count; 24 to a secondary pyrexia associated in 3 with 1 severe, 1 mild and 1 doubtful case of encephalopathy, in 2 with nine-day erythema, and 2 with other symptoms. Treatment was adjusted in 7 others for skin complications, 5 on account of headaches and in 6 others for a variety of symptoms.

There was no case of jaundice though 19 had transient urobilinogen in the urine and treatment was not modified. The incidence of Herxheimer reactions was not affected according to the duration of the disease though secondary cases generally required the treatment to be modified more frequently than those of primary syphilis.

Of the very low proportion that were followed, one-third of those originally seropositive were negative at one month; two-thirds at two months, three-quarters at three and 83·6 per cent at six months.

Eighteen cases of relapse-reinfecion were observed and have been described.

Due acknowledgments are expressed to the whole of my Staff during the period of these trials and especially to Serjeant F. Stevens, R.A.M.C., and
Serjeant J. Badger, R.A.M.C., and also to Lieut.-Colonel R. H. Simon, Lieut.-Colonel B. Levy, Major R. H. Wordingham and Major W. H. Webster for their personal communications and data supplied.

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R. R. Willcox

*J R Army Med Corps* 1947 89: 49-56
doi: 10.1136/jramc-89-02-01

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