CLINICAL USES OF 2,3-DIMERCAPTOPROPAHOL (BAL). VII.
THE TREATMENT OF ARSENICAL DERMATITIS WITH
PREPARATIONS OF BAL

BY W. T. LONGCOPE, JOHN A. LUETSCHER, JR., M. M. WINTROBE,
AND VAL JÄGER

(From the Medical Clinic, the School of Medicine, Johns Hopkins University and
Hospital, Baltimore)

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The development of 2,3-dimercaptopropanol (British Anti-Lewisite, BAL) by Peters, Stocken,
and Thompson (1) has made available a potent antidote for arsenical poisoning. Study of the
chemical combination of arsenic with sensitive enzymes and cells indicated that the arsenic could,
under certain circumstances, be removed from the cells, and that enzymes could be reactivated by
the action of BAL (1, 2). BAL administered to animals exerted both protective and therapeutic ef-
fects against local and systemic injury by toxic arsenicals (1, 2). These observations strongly
suggested that BAL might be useful in arsenical poisoning in man, and cautious trials were ini-
tiated in this hospital at the end of 1942.

METHODS

Patients were admitted to a special ward which was in
part arranged for the care of civilians employed at Edge-
wood Arsenal, under contract between the Johns Hopkins
Hospital and the U. S. Employees Compensation Com-
mission, and in cooperation with the Chemical Warfare
Service. A detailed clinical study was made of these
patients both before and after the administration of BAL.
BAL was given by intramuscular injection in 5 to 10 per cent
solution in peanut oil containing benzyl benzoate (4).
Dosage was at first varied and rather small because of
the lack of information on the therapeutic and toxic ef-
effects of BAL.

Arsenic in the urine was determined by the method of
Magnuson and Watson (5) in the laboratory of Dr. H.
Eagle. Chemical analyses of the blood were made under
the direction of Dr. Mary Buell.

RESULTS

1. Dermatitis due to diphenylamine chlorarsine

A number of workers exposed to the dust of
this chemical (also known as Adamsite or DM)

1 This investigation was carried out under contract with
the Office of Scientific Research and Development, Com-
mittee on Medical Research, OEMcmr-253.

devolved intractable dermatitis involving the ex-
posed areas of the face, neck and arms. Most of
these patients gave a positive patch test to DM. The
itching, burning, erythematous and papular eruption proved resistant to ordinary forms of
treatment. They were therefore transferred from Edgewood Arsenal to our special ward for in-
vestigation. In 6 of the 7 patients, the dermatitis had persisted for 18 to 50 days before they were
admitted to the hospital.

The application of BAL in ointment caused in-
tense burning of the affected areas, but this lasted
for less than an hour, after which the patients
received great relief from the previous itching and
discomfort. Daily applications were made, be-
ning with as low as 100 mgm., and increasing
to 500 mgm. per day in each case. The dermatitis
cleared completely in from 2 to 8 days, with an
average of a little over 5 days. The patients
served as their own controls in these studies,
since the eruption had been present for very dif-
erent lengths of time before treatment, and had
failed to respond to other forms of therapy (re-
moval of irritant and application of boric ointment
and BAL ointment base) prior to the use of BAL.

In attempting to conduct controls during the
course of these observations, BAL in ointment
was applied to the lesion on one arm, and the
ointment without BAL to the lesion on the op-
posite arm. Both lesions healed with about equal
rapidity. It was known that BAL is absorbed
readily through the skin and it therefore occurred
to us that the improvement might be due to the
systemic action of BAL as well as to its local
effect. BAL was therefore applied to unaffected
portions of the skin. These inunctions caused no
discomfort and therefore comparatively large
amounts of ointment could be employed. The re-
results were highly satisfactory, and the dermatitis
cleared under this method of application as rapidly as when the inunction had been made to the eruption itself.

The arsenic excretion in the urine increased during treatment (6), suggesting that arsenic had been released from combination with the cells.

2. *Arsenical dermatitis occurring during anti-syphilitic therapy*

Fifteen patients referred to the hospital from several clinics because of exfoliative dermatitis produced by anti-syphilitic arsenical drugs have been treated with BAL. Four of these patients received daily inunctions of BAL in ointment (5 to 10 per cent) for periods of 3 to 11 days. The average daily dose of BAL was 500 mgm. The application of this ointment was extremely painful and in one instance so agonizing that morphine was required. The exquisite pain lasted from \(\frac{1}{2}\) to 2 hours, but the relief from itching and burning was so marked within 12 to 24 hours that the patients often asked for further treatments. Applications had to be made over different areas each day, otherwise there developed a local pustular dermatitis due, we thought, to BAL itself. In many instances there was a dramatic improvement within 48 hours in the arsenical dermatitis (Figures 1 and 2).

This was often most noticeable over the area anointed.

Eleven patients were treated with intramuscular injections of BAL in 5 to 10 per cent solution in peanut oil and benzyl benzoate. The daily dose of BAL varied from 100 to 450 mgm. a day, the average being 300 mgm. Individual injections ranged from 100 to 200 mgm., averaging 150 mgm. One or more courses of treatment lasting 4 to 10 days were given.

Three patients had disagreeable symptoms from 20 minutes to 1 hour after injection of BAL. One patient complained of aching pains in the muscles of the legs, and one patient had burning of the mouth, with nausea and vomiting. These 2 patients were receiving 3.5 and 3.7 mgm. of BAL per kgm. of body weight at 6-hour intervals.\(^2\)

\(^2\) While our studies were in progress, the effects of injection of large doses of BAL in peanut oil were tested in human volunteers (4, 10, 11). The results demonstrated that a single dose of more than 3 mgm. of BAL per kgm. of body weight is likely to cause distressing symptoms, but that injections could be repeated at inter-
Symptoms disappeared when injections were stopped in one case and the dosage reduced in the other. A third patient had nausea 1/2 hour after each injection of a small dose of BAL (1.8 mgm. per kgm.). This patient had jaundice as well as dermatitis, and was probably more sensitive to gastrointestinal disturbance (1). One patient developed an abscess of the buttock at the site of an injection, an unexpectedly rare occurrence considering the distressing condition of the skin through which the injection must be made and the frequency of spontaneous abscesses.

The results are presented in Tables I and II. It is impossible in such a small series of cases to evaluate the effects of route of administration or dosage. The results appeared to be beneficial in all cases as judged by the patients' subjective reactions. Itching and burning often diminished within 24 hours, and were greatly improved in 48 hours. At about this time objective improvement in the skin usually became apparent and sometimes progressed to rapid and complete healing of the dermatitis within as few as 6 days. More often some evidences of the dermatitis persisted and complete healing occurred only after several weeks. During this time the patients' complaints were much relieved, and the skin showed only residual changes rather than continuation of inflammation. The dermatitis in 5 patients was prolonged because of mild relapses following cessation of treatment. These relapses usually responded to a second and even third course of BAL. We received a strong impression that treatment should be continued for at least 6 days and preferably longer, since 1/2 of the patients treated for less than 6 days developed a relapse of the dermatitis, while only 2 of the 9 patients treated 6 days or more showed a recurrence of the dermatitis.

The clinical improvement of these patients was accompanied by a considerable increase in the excretion of arsenic in the urine (6). A similar increase followed a second or third course of BAL during treatment of the relapses.

The observation that relapses of the dermatitis might occur when treatment by BAL was discontinuous is important since large amounts of BAL may be given in this way.

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<table>
<thead>
<tr>
<th>Complications</th>
<th>Duration of dermatitis after 1st BAL</th>
<th>No. of courses of BAL</th>
<th>Total Cystis</th>
<th>None</th>
<th>Cataneous abscesses</th>
<th>12 days</th>
<th>19 days</th>
<th>4 days</th>
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<p>| Date of adm. | No. Sex Age | Color | Doses | Amount | Arsenical | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphne min | Neera haphnem|</p>
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<th>Sex</th>
<th>Age</th>
<th>Col.</th>
<th>Arsenical</th>
<th>Amt.</th>
<th>Dosages</th>
<th>Onset of dermatitis after last dose</th>
<th>Duration of dermatitis before adm.</th>
<th>Extent of dermatitis</th>
<th>Duration of treatment</th>
<th>Total BAL</th>
<th>Re-</th>
<th>No. of courses of BAL</th>
<th>Duration of dermatitis after 1st dose BAL</th>
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<td>38</td>
<td>C</td>
<td>Neoarsphenamine 2nd course</td>
<td>0.3</td>
<td>grams</td>
<td>1-1 days</td>
<td>6 days</td>
<td>++++ Generalized exfoliative, T. 102 to 105</td>
<td>1st C. 3</td>
<td>0.3</td>
<td>1</td>
<td>2 days</td>
<td>14 days</td>
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<tr>
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<td>F</td>
<td>25</td>
<td>W</td>
<td>Mapharesen 2nd course</td>
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<td>grams</td>
<td>2 Day of last dose</td>
<td>2 days</td>
<td>++++ Generalized edema, erythema papular T. 102</td>
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<td>0.85</td>
<td>0</td>
<td>1 days</td>
<td>9 days</td>
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<td>19</td>
<td>W</td>
<td>Neoarsphenamine 2nd course</td>
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<td>grams</td>
<td>6 Day of last dose</td>
<td>10 days</td>
<td>++++ Generalized exfoliative, red T. 99 to 101</td>
<td>1st C. 4</td>
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<td>2</td>
<td>3 days</td>
<td>39 days</td>
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<td>38</td>
<td>C</td>
<td>Mapharesen 2nd course</td>
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<td>grams</td>
<td>5 2 days</td>
<td>8 days</td>
<td>+++ Vesicular, arms and face</td>
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<td>1.35</td>
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<td>Neoarsphenamine</td>
<td>3</td>
<td>grams</td>
<td>7 3 days</td>
<td>8 days</td>
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<td>1.8</td>
<td>0</td>
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<td>grams</td>
<td>3 11 ? days</td>
<td>11 days</td>
<td>++++ Generalized maculopapular erythema weeping T. 101</td>
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<td>grams</td>
<td>4 8 days</td>
<td>15 days</td>
<td>++++ Generalized exfoliating edema T. 102 to 103</td>
<td>6</td>
<td>2.35</td>
<td>0</td>
<td>1 days</td>
<td>Perineal abscess. Abscesses of skin, multiple; fever 2 months. Penicillin</td>
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<td>M</td>
<td>36</td>
<td>C</td>
<td>? 2nd course. History of dermatitis</td>
<td>?</td>
<td>grams</td>
<td>3 After 2nd dose</td>
<td>3 days</td>
<td>++++ Generalized edema, erythema papulo-vesicular T. 99.6 to 101</td>
<td>10</td>
<td>4.3</td>
<td>0</td>
<td>1 days</td>
<td>Abscess of buttocks</td>
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<td>Neoarsphenamine</td>
<td>?</td>
<td>grams</td>
<td>6 After 1st dose</td>
<td>21 days</td>
<td>++++ Generalized vesicular crusting, weeping T. 100.8</td>
<td>7</td>
<td>2.85</td>
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<tr>
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<td>grams</td>
<td>4 2 days</td>
<td>35 days</td>
<td>++++ Generalized T. 100.2</td>
<td>8</td>
<td>1.8</td>
<td>0</td>
<td>1 days</td>
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continued, but could be controlled by reinstituting treatment, and that the excretion of arsenic in the urine increased during each course of treatment by BAL, but decreased rapidly each time that the administration of BAL was omitted. suggested very strongly that there was a relationship between the 2 sets of conditions. Such a correlation might be interpreted as an indication that the intra-muscular injections of BAL resulted in a liberation of arsenic from the tissues of the body, and that this release of arsenic was followed by clinical improvement.

**DISCUSSION**

We have been very favorably impressed with the response to the administration of BAL in exfoliative dermatitis. The patients described a considerable relief of symptoms. The objective improvement was often equally impressive, but complete healing was frequently delayed for several weeks. It may be possible to eliminate the mild relapses which prolonged the course of $\frac{3}{8}$ of our patients, by continuing the treatment for as long as a week or more after the initial rapid improvement occurs.

In addition to the relief of the patient's symptoms and the objective improvement in the skin after the use of BAL, we had the impression that the patient's illness was shortened. Because of the variability of the disease, it is difficult to obtain any accurate information on the duration of arsenical exfoliative dermatitis. It is said to last "seldom less than 8 weeks and often as long as 12 or more" (7).

During the past 20 years, 49 patients have been admitted to the Johns Hopkins Hospital for arsenical exfoliative dermatitis, and have been followed throughout the course of the disease in the hospital and its out-patient department. The precipitating agents were neoarsphenamine (23 cases), arsphenamine (10 cases), mapharsen (3 cases), and in several cases the less commonly used

**Fig. 3. Comparison of the Total Duration of Exfoliative Dermatitis in 49 Attacks in 46 Patients Not Treated with BAL, with the Total Duration in 15 Comparable Patients Treated with BAL**

Open squares: Patients receiving 1 or 2 injections, often small test doses, of arsenical drug. Shaded squares: Patients receiving 3 or more therapeutic doses of arsenical drug.
arsenical drugs. There was no evidence that the dermatitis produced by one of these arsenicals differed in severity or duration from the group as a whole. It is clear, however, that dosage and repeated injections may affect the duration of the reaction. Figure 3 shows that exfoliative dermatitis following only 1 or 2 injections of arsenic (often small doses because of suspected hypersensitivity) was frequently quite brief, in contrast to the generally more prolonged course in patients who received 3 or more therapeutic doses of an arsenical drug. Three deaths occurred in this latter group of 36 patients.

The dermatitis in the patients treated with BAL was probably of somewhat greater average severity than in the control group. The patients were admitted to the hospital at about the same time (average of both series was the 10th day).

In the group treated with BAL, there were a number of patients who recovered with unexpected rapidity (Figure 3). This difference from the control series is most evident in the patients who received 3 or more therapeutic doses of arsenic. On the other hand, the cases who received smaller and fewer doses might have recovered spontaneously at this time, and little can be said about the effect of BAL on the duration of the disease. No deaths occurred in the 15 patients who received BAL, although 3 deaths occurred in the control series of 49 patients and far higher mortality rates have been reported in patients with severe exfoliative dermatitis (8, 9).

**SUMMARY AND CONCLUSIONS**

Twenty-two cases of arsenical dermatitis have been treated with 2,3-dimercaptopropanol (BAL).

Seven of these patients with an intractable, localized dermatitis caused by diphenylamine chlorarsine improved within a few days after the inunction of BAL in ointment.

Fifteen cases of generalized, exfoliative dermatitis following the use of antisyphtilitic arsenicals have been treated with inunction or injection of BAL. Symptomatic and objective improvement regularly followed the administration of BAL. The duration of the dermatitis in over ½ of the patients treated with BAL was shorter than in a comparable group of patients who were not treated with BAL.

A mild recurrence of the dermatitis was frequent when treatment was not continued for at least 1 week. Six such relapses cleared quickly after reinstitution of therapy.

BAL in ointment was quite painful when applied to inflamed skin, while intramuscular injections were much less disturbing. No serious constitutional reaction to BAL was observed with the small doses employed.

**BIBLIOGRAPHY**