TREATMENT OF GONORRHOEA AND SOFT CHANCRE IN EGYPT
BY SULPHONAMIDE.

BY MAJOR L. B. CLARKE,
Royal Army Medical Corps.

WITH A NOTE ON THE BLOOD PICTURE

BY MAJOR D. W. BEAMISH, M.C.,
Royal Army Medical Corps.

The introduction about two years ago of chemotherapy into the treatment of gonorrhea and its more recent adoption for that of soft chancre, are milestones on the road of medical progress and rank with the discovery of salvarsan. Both gonorrhea and soft chancre in the absence of a specific drug have proved for many years problems of the first order whose solution appeared to be well-nigh impossible.

The former, through its incidence and chronicity, accounted for more bed space in our military hospitals than any other disease and much loss of man power to the Army, and the latter in lesser degree also presented a very difficult problem.

The discovery of the prontosil group of drugs has completely altered the outlook, and the barometer is set fair for further progress.

In view of the fact that the only account so far published in the Journal relates to work done in England, it is thought that a record of the observations carried out during the last nine months in Egypt may prove of interest to those whose professional duties may include the treatment of venereal disease.

The opinions expressed are purely personal ones, and are put forward very largely for the purpose of inviting criticism or confirmation.

The drug used has been Messrs. Burroughs Wellcome's Sulphonamide in 0.5-gramme tablets.

GONORRHOEA

For purposes of comparison it is interesting to note briefly the previous attempts made in this Centre to lower the average stay in hospital. It must, however, be borne in mind that the Citadel Military Hospital at Cairo by no means provides ideal accommodation, and that conditions in this old building are not favourable for rapid recovery, and it is expected that the average time to cure gonorrhoea will always be greater than elsewhere.

On my arrival in this country in 1935 the average stay in hospital proved to be the very long one of seventy days.

Two types of experimental treatment, originated by me, were carried out:—
In 1935-36 irrigations by saline 1 per cent and sodium sulphate 5 per cent took the place of potassium permanganate. Previous experience in Rangoon and Aldershot had convinced me of the value of the alternative treatment, and two communications on this subject had already appeared in the Journal [2], [3], and had been commented upon by the British Medical Journal [4], [5], and the Military Surgeon [6]. In Cairo this treatment brought the average stay in hospital down to 55.3 days, a much longer time than in previous stations.

In 1936-37 this form of irrigation was continued, and protein shock in the form of increasing doses of intravenous T.A.B. at four-day intervals was instituted and lowered the stay in hospital to 43.3 days.

These two forms of experimental treatment are recorded as showing that some effort had been made to cope with the problem, and that some improvement had taken place although the figures were still very high. This was the situation existing at the time of the introduction of sulphonamide.

In April, 1938, there was a small stock which had been ordered for the general wards, and in view of the publication of two articles, one by Dr. A. J. Cokkinis [7] in the British Medical Journal and the other by Lieutenant-Colonel O. J. O'Hanlon, [1] R.A.M.C., in the Journal of the Royal Army Medical Corps, it was felt that a trial should be made in Cairo.

A number of old-standing chronic cases were selected, and the treatment met with immediate success, forty-one cases out of forty-five leaving hospital after a ten-day course and successfully passing their test for cure.

The results were so encouraging that a stock of 75,000 doses was asked for. In the meanwhile I had the opportunity, whilst on leave in England, of discussing the problem with Lieutenant-Colonel O’Hanlon, who stressed the point that the dose had to be pushed almost to toxic limits to effect a cure, an opinion amply borne out by the subsequent work in Cairo.

The observations which are now recorded commenced at the beginning of July, 1938, and cover a period of nine months. The details of dosage and administration largely follow those recommended by Lieutenant-Colonel O’Hanlon.

**Standard Course of Treatment.**

The standard course of treatment consisted in administering the drug by the mouth four times daily at evenly spaced intervals: 6 a.m., noon, 6 p.m., and midnight.

The following number of tablets were given per day: 12, 12, 12, 12, 8, 8, 6, 6, 6.

This constituted a ten-day course which commenced two days after admission.

The diet consisted of a fairly generous "light" diet from which was excluded eggs and onions, owing to their sulphur content. Aperient salts were withheld for the same reason, and cascara or castor oil substituted.
The question of irrigations naturally arose as there was no guidance on this point from any of the publications on the subject.

The plan finally evolved was to avoid irrigations within the first five days. If, however, the discharge was not at that stage clearing up, 1 : 20,000 potassium permanganate was started. Saline and sodium sulphate irrigations have not so far been used owing to the complicating factor of sulphur, although the amount absorbed cannot be very great.

Although this was the general scheme of treatment which the majority of the patients received, it was, however, modified in a minority of cases in two ways: (1) A few cases did so well that treatment was suspended after five or six days with complete recovery; (2) cases showing complications of a severe type were stopped permanently, and of a mild type temporarily.

The test for cure adopted for all cases was the routine one of previous years: Case "dry" for four days, cessation of all treatment, two bottles of beer a day for two days, one cubic centimetre of gonococcal vaccine, and a prostatic massage. If the case were then still absolutely "dry," discharge from hospital took place two days later. It is thus seen that a period of eight days was allowed before the man was returned to his unit. All men were recommended four days' excused duty and three days' light duty, and given a warning to avoid alcohol, violent exercise, and all excitement of a prejudicial nature. Cases reported to hospital weekly for a surveillance lasting from six weeks to two months.

For the first five months of the period under review differential blood-counts were done by Major D. W. Beamish on the fourth and eighth days of treatment to maintain a check on the condition of the blood. One case only suggested the onset of agranulocytosis. The scheme was modified in the last few months to the extent of only doubtful cases being tested, as it was by this time considered that the clinical picture in the ordinary course of events provided an adequate safeguard.

Major Beamish has kindly written a short account of this work for inclusion in this article.

RESULTS.

The results have far exceeded anticipation and are analysed in Table I. This shows the number of courses necessary to effect a cure and the average stay in hospital. The total number of cases treated by sulphonamide is 224.

<table>
<thead>
<tr>
<th>Number of ten-day courses</th>
<th>Number of cases</th>
<th>Average number of days in hospital</th>
<th>Days in hospital with relapse</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>One course</td>
<td>150</td>
<td>18.8</td>
<td>27</td>
<td>Cyanosis: 132, Temperature: 70, Rash: 16</td>
</tr>
<tr>
<td>Two courses</td>
<td>52</td>
<td>44.7</td>
<td>6</td>
<td>Cyanosis: 47, Temperature: 17, Rash: Nil</td>
</tr>
<tr>
<td>Three courses</td>
<td>21</td>
<td>69.3</td>
<td>1</td>
<td>Cyanosis: 20, Temperature: 4, Rash: Nil</td>
</tr>
<tr>
<td>One long case</td>
<td>1</td>
<td>89.0</td>
<td>Nil</td>
<td>Cyanosis: 1, Temperature: Nil, Rash: Nil</td>
</tr>
<tr>
<td></td>
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L. B. Clarke and D. W. Beamish

Classification of Results.

(1) Good results, requiring one course, 150 cases leaving hospital in 18.8 days.
(2) Fair results, requiring two courses, 52 cases leaving hospital in 44.7 days.
(3) Bad results, requiring three courses, 21 cases leaving hospital in 69.8 days.
(4) One long case, requiring four courses, and leaving hospital in eighty-nine days.

Notes on the Above Classification.

(1) Good Results.—These 150 cases, which did very well, were nearly all "dry" on the fifth day, the gonococci having disappeared from the smears by the third day. Some cases were actually "dry" on the third day, i.e. after only two days' treatment.

(2) Fair Results.—These 52 cases cleared up soon after the second course with a stay in hospital of 44.7 days, and probably represent an average time without sulphonamide.

(3) Bad Results.—These 21 cases required three full courses and remained in hospital 69.4 days. These and the one very long case naturally prompt the question as to why they have not responded to treatment, and this point is discussed below. Twenty-seven cases relapsed and were in hospital twenty-seven days.

Discussion on Sulphonamide Failures.

At the outset there was no special factor observed which might in any way distinguish these men from those who made a quick recovery, and the reason remains somewhat of a mystery.

In order to try and discover any common factor in these cases a careful perusal of the clinical notes was made, and it is interesting to observe that:
(1) They had nearly all been out in Egypt more than two years. (2) Their average service was about six years, i.e., within a short time of completing an average engagement. (3) They were nearly all above the average age of the serving soldier. Many were rather senior N.C.O.s.

By contrast, those who did best were mostly young soldiers, and these went out of hospital in from fourteen to eighteen days.

Alcohol, employment, previous general condition, and place of origin of disease were all considered, but appeared to have no bearing on the subject, and the only conclusion so far arrived at is that generally speaking the younger soldiers do better than the older.

It would be a matter of great interest if other medical officers who have had experience of sulphonamide could throw any further light on this subject as it is definitely one about which we are at present very much in the dark.
Complications due to Treatment.

There were three main varieties of complications due to treatment and several minor ones. Taken in order of frequency there were:

1. **Cyanosis.**—Most of the cases became cyanosed in varying degree, no less than 200 out of 224. The shade varied from a faint blue to a deep plum colour, especially marked on the lower lip. The fainter shades were regarded as normal, but the deep plum colour, especially when associated with an ashen grey coloured face, called definitely for cessation of treatment. A curious point is that headache and giddiness were often absent in severely cyanotic cases.

2. **Temperatures.**—91 out of 224 cases developed temperatures varying from 100° to 103°, usually about the fifth day, but quite often just at the end of the course. The drug was always stopped, the fluid part of the diet increased, and the temperature fell to normal within twenty-four to forty-eight hours. In some cases a second course was given after about ten days' rest with no apparent harm.

3. **Rashes.**—16 cases developed rashes. They showed at about the fifth to ninth day on the extensor aspect of the arms and forearms, the front and back of the chest, and less frequently on the face. The rash consisted of small, polymorphic, discrete macules. The colour varied according to the degree of cyanosis from pale blue to deep plum. In those with no cyanosis it was pink. No papules were seen. This complication was regarded as a definite toxic sign and sulphonamide was stopped permanently. An increase in the fluid part of the diet by soda water and lemonade and a further additional quantity of barley water appeared beneficial. The rashes in all cases cleared up in three days and the patients seemed none the worse. The differential diagnosis of these rashes from those of syphilis and the exanthemata would afford an interesting intellectual exercise.

4. **Minor Complications.**—In order of frequency these were: (a) **Headache:** Most patients complained of varying degree of headache which came to be regarded as almost normal, and no treatment was given as it appeared unwise to add a further depressant drug to sulphonamide. If, however, any reasonably safe analgesic is known, such information would be welcomed. (b) **Constipation:** Many cases became very constipated, partly through being in bed. As the saline aperients contain sulphur they were withheld, and cascara or castor oil substituted, many soldiers having a preference for the latter. (c) **Vertigo:** It was a common feature in many cases for attacks of sudden giddiness to be reported, especially when getting out of bed. This did not call for any special attention other than to issue a warning to go slowly. (d) **Pain in Chest and Stomach:** This was uncommon and was said to resemble heartburn and disappeared with bicarbonate of soda. Only a few cases of vomiting occurred.

All complications cleared up well after three days, and except for rashes did not constitute a contra-indication to a further course if such were necessary.
It should, however, be realized that a highly toxic drug is being used, that there is a fine and variable margin between cure and danger, and that the nearer one approaches to cure the greater is the danger. Each case therefore, requires careful observation, and a daily review of the degree of toxicity and its relation to the progress of the disease.

Cases on sulphonamide should definitely be in bed throughout the course and a strict control of the drug maintained to ensure that it does not fall into unauthorised hands.

As a further measure of safety all cases were kept in bed for at least two days after cessation of treatment, during which time the special egg-free diet was continued.

Complications of Gonorrhoea Arising During Treatment.

Two cases of epididymitis occurred; a great improvement compared with previous forms of treatment. These complications are particularly common in the East and often require a long period for recovery. It is striking testimony to the new drug that so few of these complications occurred.

There were two cases of arthritis, one of which was severe and was invalided to England.

There is no doubt that sulphonamide cuts down the incidence of epididymitis, but it had no effect whatever in preventing the case of arthritis, which had to be invalided. This case is referred to below as one which at an earlier stage had developed double ophthalmia.

Cases of Ophthalmia.

Two cases of double ophthalmia arose during treatment. One was the arthritis case referred to above, and it is thought that this was of metastatic origin. Both these eye cases made dramatic recoveries as regards the ophthalmic signs with four days of sulphonamide treatment at the rate of twelve tablets a day. The usual routine local treatment was, of course, carried out as well.

Relation between Dosage and Body-weight.

Occasionally the dosage was reduced for men of small physique. On the other hand, a corporal of one of the Guards' regiments, who was 6 feet 5 inches in height and weighed 17 stone, did not appear to be doing well on the routine dosage and it was thought that he was not getting sufficient for his body-weight. On the third day, after two days of twelve tablets each, the dosage was increased for the remainder of his treatment as follows: 15, 16, 16, 16, 16, 16, 16. He thus had 151 tablets representing a total of 75.5 grammes of the drug. He was "dry" on the fourth day and did very well. This case is recorded as showing the very large dosage which may be tolerated by a big man. Only slight cyanosis occurred.
Treatment of Gonorrhœa and Soft Chancre by Sulphonamide

Soft Chancre.

With the full possibilities of sulphonamide still unexplored, it was thought that other diseases in a dermatological centre might react favourably, and in the absence of a specific drug for soft chancre this disease was selected for experiment.

This condition as seen at home and abroad would appear to be almost two different diseases, certainly as regards incidence and response to treatment.

At home it is a comparatively rare disease, abroad it is common, forming 106 cases out of a total of 665 admitted to the Citadel Military Hospital last year.

At home it tends to clear up fairly quickly, abroad it is definitely a chronic condition, often accompanied by buboes of a painful and intractable nature.

Our chief assistance in the past has come from dmelcos, which given intravenously clears up a number of cases in a satisfactory manner, but its value is limited and somewhat uncertain, and it has not been used very much in this centre recently.

During the past year sulphonamide was introduced for the soft chancre cases at the same time and in the same dosage as for gonorrhœa.

The results are summarized in Table II. It should be pointed out that the word "routine" for the first six months does not include dmelcos, so that sulphonamide is not compared with this drug.

<table>
<thead>
<tr>
<th>Period</th>
<th>Treatment</th>
<th>Number of cases</th>
<th>Number of days in hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>January—June, 1938</td>
<td>Routine</td>
<td>35</td>
<td>28.0</td>
</tr>
<tr>
<td>July, 1938—March, 1939</td>
<td>Sulphonamide</td>
<td>111</td>
<td>15.8</td>
</tr>
</tbody>
</table>

It will be seen that sulphonamide caused a reduction in the length of stay in hospital from an average of 28 to 15.8 days.

As these cases were naturally all under observation for syphilis, saline was given as a local dressing for four days and then eusol. The dark-ground tests and later the routine Wassermann or Khan tests were all negative, and after the usual three months' observation and tests these cases were finally diagnosed soft chancre.

It is interesting to note that two cases of syphilis, closely resembling soft chancre with negative dark-ground tests, were placed on sulphonamide with no effect whatever on the sores. At a later stage the blood-test proved the presence of syphilis, and as a matter of interest further dark-ground tests were done. The spirochaetes then seen were numerous, active and healthy, so it was definitely established that sulphonamide has no power over the spirochaete nor does it appear to affect the blood-test in any way.

A further interesting point emerged from these two cases. The dark-ground fields, although showing plenty of spirochaetes, were entirely clear of other organisms, debris, and extraneous matter. It seemed as though sulphonamide had cleared the ground for the spirochaetes.
One of the most satisfactory features of sulphonamide in cases of soft chancre is the dramatic fashion in which commencing buboes clear up and disappear often in forty-eight hours. No case of bubo arose during treatment. The relief of local pain is also a prominent feature.

If sulphonamide had done nothing else than eliminate epididymitis and buboes from our venereal practice it would have formed a veritable milestone in medical history.

It is also to be noted that whilst there was a varying degree of response to the drug there was not the wide discrepancy between good and bad results as there was in gonorrhoea. In fact most of the cases reacted very favourably and without complications.

A final interesting point emerged during the course of the nine months' observation, and this was the "discovery" that sulphonamide may be applied locally to the sores, either during or after the course of treatment. As it is only slightly soluble in water it is probably mostly in the form of a suspension. It remains on the sore for some time as a caked white powder very much like calamine lotion. The results are nearly always excellent and sometimes dramatic.

It would seem that sulphonamide is really far more effective in this disease than in gonorrhoea, and its usefulness in soft chancre has been obscured by the comparative incidence of the two diseases.

CONCLUSIONS.

Sulphonamide in doses sufficient to produce a certain degree of toxicity is shown to be a most powerful agent in the treatment of gonorrhoea, two-thirds of the cases leaving hospital in less than nineteen days, the remaining third failing to respond to the same extent, and a few appearing to be entirely unaffected by its administration.

In soft chancre also excellent results were obtained by the drug when given on the same lines as for gonorrhoea, but with less uncertainty as to cure and less toxicity.

It is thus seen that we have now at our disposal a group of new drugs, one of which at any rate has very marked therapeutic powers.

M & B 693 has recently been taken into use in this centre, and while it is too early to draw definite conclusions from the small number of cases so far treated, two effects appear to be emerging: (1) Excellent results with some cases; (2) during the hot and humid weather now prevailing in Egypt several cases have developed severe rashes, one of which was the most marked I have ever seen.

If this or any other new drug in this group should be found to have equal therapeutic powers and be less toxic, the problems which have for long beset the path of the dermatologist may recede into the limbo of the vanished past.
NOTE ON THE BLOOD PICTURE.

By Major D. W. Beamish, M.C.,
Royal Army Medical Corps.

The following is a résumé of differential blood-counts performed on gonorrhoea and soft chancre cases under treatment by sulphonamide:—

<table>
<thead>
<tr>
<th>Total number of counts</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>330</td>
</tr>
<tr>
<td></td>
<td>187</td>
</tr>
</tbody>
</table>

Out of the 187 patients there were 33 who showed a lymphocytosis, 6 of them being over 40 per cent and one 68 per cent.

14 cases had a polymorphonuclear leucocytosis, i.e. 80 per cent.

8 cases had a eosinophilia, i.e. 7-12 per cent.

3 cases had a monocytosis (increase in the large hyaline cells), i.e. 15-20 per cent.

Perhaps the most interesting point arising out of these blood-counts is the fact that only 17.6 per cent showed any abnormality in the differential count in spite of the fact that large amounts of the drug were given and a number of the patients developed symptoms such as cyanosis, high temperature, and rash.

The first abnormality usually noticed under the microscope was a diminution of the percentage of the polymorphonuclear leucocytes and a corresponding relative increase in the mononuclear variety.

In general the cases which had complications had a lymphocytosis and in one case only was there a definite tendency to the condition of agranulocytosis.

On the whole we have found it useful to have routine counts done as a check on the treatment, but as clinical experience of these cases increases and as the pathologist becomes more conversant with the blood pictures, the number of routine tests may be cut down considerably.

After a little practice one can inspect a well-stained film in a few minutes, and at a glance the picture is sufficient to decide whether or not any gross abnormality is present.

In other words a complete differential count worked out in mathematical detail is not necessary.

In two cases treatment was stopped and in one case reduced, as a result of the blood-counts.

The cause of the eosinophilia cases is not accounted for. A concurrent helminthic infection was a possibility.

Where leucocytosis and lymphocytosis are mentioned the increase is presumed to be relative, as in only a few cases were total counts carried out, and these showed little or no change, or some increase, due to the disease and intensity of infection, etc.
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