Summary

A case of gumma of the thyroid gland is reported and the literature is reviewed.

I am indebted to Dr. J. Laurie, Medical Superintendent, Sharoe Green Hospital, Preston, Lancashire, for the radiological investigation and reports of the case reported on by myself.

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INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS*

By T. R. LLOYD JONES, M.R.C.S., L.R.C.P.

Surgeon Captain, Royal Navy; Consultant in Venereal Diseases, Royal Navy

and F. GORDON MAITLAND, M.R.C.S., L.R.C.P.

Surgeon Lieutenant Commander, Royal Naval Volunteer Reserve

Since World War II began a notable increase in the incidence of venereal disease has been recorded, bringing in its wake sociological and economic consequences. In the Forces these problems, especially as regards early syphilis, brought us to the point at which it was undoubtedly necessary that previous methods of treatment, often involving a big wastage of man-hours, should be revised, in order that some saving could be made in this direction and that men suffering from syphilis could be cured as quickly as possible. This problem

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INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS

affects us in the Forces probably much more than it would in civil life, because men in the Forces are expected to be fit in every respect for active duty.

American methods of treatment

Chargin, Leifer, and Hyman, by their pioneer work on intensive arsenotherapy published in 1935, opened up a new field of treatment for syphilis, and from that date to the present time varying methods of intensive treatment have been used.

The following may be quoted as examples of methods of treatment with mapharsen which have been carried out to date in the United States of America.

(1) One-day treatment in which fever therapy and mapharsen were used with or without heavy metals.

(2) From 5 to 8 days' treatment by varying methods.

(3) From 10 to 20 days' treatment by multiple syringe injections, with or without fever therapy.

(4) Treatment of 6 weeks' or longer duration in which the frequency of injections varied from 2 to 3 each week and the total length of the course varied from 6 weeks to 6 months; heavy metals were usually included. The American Army plan of 40 mapharsen and 16 bismuth injections in a period of 26 weeks is a compromise between the short intensive system and the 70 weeks' standard regimen.

Endeavours are being made to evaluate these different methods so as to establish some form of adequate standard treatment for general use.

Moore states that the satisfactory curative dose of mapharsen—that is to say that dose which will presumably render 85 per cent of patients with early syphilis permanently sero-negative—seems to be largely independent of the method of administration, and to be about 20–30 milligrams per kilogram of body weight, or a total of between 1,000 and 2,000 milligrams for a man weighing 50–70 kilograms. Attempts to use less mapharsen, whether by intravenous drip or by multiple injections, have given unsatisfactory results. An infinite number of permutations of time, dosage and frequency are possible, each with a calculable margin of safety and correspondingly predictable incidence of serious toxic reactions. If this laid-down curative dose of mapharsen is given within 10 days or less, serious reactions and a high rate of mortality occur, which are both excessive and unnecessary. From data accumulated on 5,000 cases treated by intensive therapy within a 1–10 day period, it was found that there were 25 recorded deaths, that is to say one death in each 200 patients treated. This rate is much too high and the method far too dangerous for general adoption. The cause of death is generally toxic encephalopathy.

Categories of primary syphilis

We say that this fixed predetermined laid-down dosage is unnecessary; it has been used because, with the commonly accepted methods of treatment by intensive arsenotherapy, no attempt has been made to determine the exact diagnosis or category of the early primary group.

Moore himself says: "It is unfortunate that no method exists by which the probable cures after small amounts of treatment can be picked out before or during treatment, and that this hiatus in our knowledge is responsible for the undoubted fact that some patients receive much more treatment than is actually necessary." We believe that our re-categorization of early syphilis into three separate and recognizable groups, as proved by the quantitative serological test for syphilis in each individual case, is probably the solution to this problem.

It had been noticed occasionally that, as a result of Service duties, men were moved away after receiving a few injections only and that, although no further treatment had been given, their blood tests had remained consistently negative over a period of many years. A number of the cases thus treated were investigated, and it was found that a considerable percentage of these men, who had received certainly not more than a single course of injections, had been cured. Padgett¹ states that patients who receive as little treatment as 4–6 injections have a 60 per cent chance of a five-year cure; this confirms our observations. Further investigation of our cases showed that it was the men with negative blood tests

before and during treatment who were the fortunate ones, but until now we had not had the opportunity of trying to establish the observations on a scientific basis.

In February 1943 we began a trial of intensive arsenotherapy. At the beginning of our investigations a qualitative Wassermann test (by the McKenzie-Browning technique) was being carried out, but we were most anxious for the substitution of a more sensitive test in the form of a quantitative method. It was hoped that by means of this test the degree of intensity of infection could be judged and that the treatment could be regulated accordingly. With the helpful co-operation of Surg. Lieut. Cdr. Sloan Miller at Haslar, the Kolmer-Wassermann quantitative test, as carried out in the United States of America, was substituted for the qualitative test.

Utilizing this daily quantitative test, it was found that early syphilis—so called primary syphilis—fell into three main groups (Jones and Maitland¹).

Group 1.—"Early primary" syphilis, in which the daily serological test remained consistently negative throughout the treatment.

Group 2.—The group that we called "middle primary", which began with a negative serological reaction, but in which a sudden short positive phase lasting up to a few days developed, after which the reaction reverted to negative.

Group 3.—"Late primary", in which the titre was high initially and either remained consistently high for some time following treatment before falling, or gradually fell during the actual treatment.

By means of this re-categorization we had a reliable guide which, up to date, as far as we are aware, has either been ignored or not recognized, but which, we feel, is of the utmost importance, as it opens a new vista of primary syphilis from the point of view of diagnosis, prognosis and treatment.

Serological basis of categorization

Groups 1 and 3, that is "early" and "late" primaries, presented no sero-diagnostic difficulty, but group 2, "middle primary," is, we feel, of some real significance; for when serum control is not performed frequently, or better still daily, it is often unrecognized.

To what is this short and temporary rise in serum titre due? We are convinced that this positive phase is not a finding due to a technical error within the limits of the test; neither do we consider it to be connected with a Herxheimer reaction; only 4 of the "middle primary" cases had a true Herxheimer reaction. It does not seem to be due to any provocative drug action; the existence of such a provocative effect after an injection of arsenic is now disputed and the theory considered to be fallacious; therefore, some explanation should be attempted. Kahn has expressed the opinion that in the sero-negative stage of early syphilis the serological test is negative because there is a state of balance, or neutralization, between the antigen produced by the spirochaete and the reagin produced in response by the patient. A positive serum state is reached when the reagin content of the patient's serum is in excess of the antigen. This positive serum state may be due to the following factors.

- (1) Removal of the spirochaetes by treatment, leaving free reagin.
- (2) Reagin being produced in excess of antigen.
- (3) In late syphilis, to the patient's natural immunity being developed, and so again reagin being produced in excess of antigen.

Applying this theory to our "middle primary" group, it follows that the initial balance of reagin versus antigen, giving the early negative serological reaction, is altered by the rapid removal of the spirochaete by treatment. Reagin does not disappear from the serum as quickly as does antigen, and this causes a temporary unbalanced positive level of reagin, showing itself in the slight rise in serum titre. As the reagin-producing stimulus (antigen) has been removed and has not been present over a long period, this unbalanced phase of reagin is not maintained; reagin ceases to be produced so the serum titre rapidly reverts to negative—the negative of a serological cure. Without treatment the titre would surely have risen quickly to the high level of the "late primary" a

INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS

reaction that we have seen in certain of our "late" primary cases with a long incubation period.

If the above explanation is accepted, it shows quite clearly that our assumption in referring to the "middle" primary as a stage intermediate between "early" and "late" is justified. It is, we think, representative of a definite stage in the evolution of the "late" primary case which has been aborted by treatment—treatment which is slightly more than the aborting dosage necessary for the "early" primary, but not as large as the curative dose required for the "late" primary. It is difficult to see the reason for the generalization that these "middle" primary cases are always the result of a Herxheimer reaction.

Rationale of treatment

The approach to the practical side of any treatment scheme is always difficult because we are all apt to be highly critical of each other's methods and technique, so we ask for tolerance of anything that is suggested.

Published papers on the subject of arsenotherapy have reported all types of cases of early syphilis, with either negative or positive blood reactions, as being treated as a whole by means of a fixed and predetermined dosage of arsenic, irrespective of the type or stage of the disease. As is stated above, we were not satisfied as to the justification or desirability of treating all cases, irrespective of type, by the same predetermined fixed standard of dosage of arsenic. The following questions arise in this connexion.

(1) Why should an "early" primary case with a consistently negative blood phase receive 40 injections, or more, of arsenic and bismuth, entailing anything from one to two years' treatment? Why should not this type of case be aborted by a relatively short course of intensive therapy?

(2) Could not a hitherto apparently unrecognized "middle" primary case be given a slightly increased dosage as compared with the "early" primary case (with which, presumably, it has been so far classified)?

(3) Lastly, could not a "late" primary case be cured by an increase in the dosage given to the "middle" primary case? In other words should not the dosage of arsenic be "stepped up" according to the blood test results?

It has been our endeavour to treat each of these categories with a dosage predetermined according to the serological results, and not with one fixed dosage. We feel that our re-categorization of early syphilis is an advance on existing ideas and, applying this principle, it has been our hope to obtain the maximum therapeutic effect with the least possible amount of toxic manifestation.

Our cases were all diagnosed primarily by the finding of *Spirochaeta pallida* in each individual case. One important point emerges from all the work done on the treatment of syphilis, and that is that the earlier syphilis is diagnosed the better the prognosis. Moore states that the cure of syphilis is much more readily obtainable when treatment is begun within the first few days of infection than when it is delayed until the appearance of a positive serological test or of outspoken secondary manifestations.

Bearing this important statement in mind, it is most essential to regard all genital lesions of any kind whatsoever, when there is a history of exposure, as potential syphilis until diagnosed otherwise. This includes scabies ulcerations, balanitis, fraenal tears, herpetic lesions, and so forth. Less reliance should be placed on text-book descriptions of a typical syphilitic sore. The finding of the *Spirochaeta pallida* is the only proper way of early diagnosis, and this entails the intelligent use of the dark-ground microscope.

Dosage according to categories

Now to discuss the question of the treatment of these various categories or types. (1) To begin with we gave the early primary group 10 injections of 0.04–0.06 gramme of mapharsen, depending upon the patient's body weight, that is a total of 400–600 milligrams. Because of a relapse in 2 cases we modified this to 15 daily injections of 0.04–0.06 gramme, giving a total of 600–800 milligrams. This has proved to be very satisfactory and we hope that it will turn out to be a more or less correct aborting dose for this "early" primary group.

(2) The next group, which we have termed the "middle" primary group, showed a short positive phase during treatment. Because of this positive phase we gave the patients 20 daily injections of 0.04-0.06 gramme of mapharsen, 5 more than to the "early" primary cases, making a total of 800-1,200 milligrams. This scheme also has proved to be satisfactory and so far has not required any modification.

(3) Lastly, the well-established group of sero-positive primary or, as we have termed it, the "late" primary group (which included the secondary syphilis cases) has been the most difficult to manage from the point of view of treatment. We began with 30 daily injections of 0.04-0.06 gramme, using a total of 1,200-1,800 milligrams, according to body weight; but some relapses occurred, both clinical and serological, so that our last 45 patients were treated with a dose proportional to their weight, that is 20 milligrams per kilogram, but with an added dose of bismuth (0.2 gramme) given every third day. The low rate of relapse incidence on this scheme has shown it to be the most suitable for the "late" primary group. It should be pointed out that these scales of treatment dosage were largely empirical and were subject to modification as experience demanded. The figures from the American reports show an average relapse rate of 12-20 per cent for all methods of intensive therapy; our average relapse rate has been 9 per cent.

Daily blood tests

The use of these has enabled us to categorize our patients without difficulty by estimating the intensity of the infection. It is realized that this result was achieved through the amenities of the Service, but if the diagnosis of early syphilis as suggested by us is accepted, frequent quantitative blood controls are needed; otherwise every patient must have the same fixed large predetermined dose—the very situation that we wish to avoid. However, if facilities are not available for a daily blood test to be performed, it is considered that blood taken on the first, fourth, seventh and tenth days of treatment will probably give a fairly reliable guide, sufficient anyway to enable one to decide the appropriate dose. It is stressed that the quantitative serological test for syphilis is of much greater value than is the qualitative test. Both the quantitative Kolmer-Wassermann and the Kahn tests were done on each blood serum and the results charted in the form of a graph which enabled us to see at a glance the progress of each patient. (Compare the graphs on p. 72 of the June issue of the *Journal*, Jones and Maitland².)

Reactions and toxic effects

Primary reaction.—The first reaction was the Herxheimer, which occurred in 4 cases. There seems to be some conflict of opinion regarding this reaction. Is any pyrexia following the first injection to be considered as a Herxheimer effect, or must it be accompanied by a local as well as a general reaction? It is in the latter regard that we have recorded these cases. Primary pyrexia over 100° F. occurred in 29 cases and was sometimes accompanied by headache and shivering, without a flare-up of the local lesions or other signs.

Later reactions.—These included secondary pyrexia, 31 cases, and toxicoderma or Milian's ninth-day erythema, 8 cases. The problem of further treatment for syphilis in cases of toxicoderma was baffling at first and, until Colonel Pillsbury and his colleagues showed us how to deal with it by desensitization, it meant the end of intensive arsenotherapy for that patient. Latterly the patient was desensitized and completed treatment.

Toxic encephalopathy.—It was on the ninth, tenth and twelfth days respectively after the patients' initial injection that 3 cases of toxic encephalopathy occurred. One was fairly severe, the others mild; fortunately none was fatal. Epileptiform convulsions heralded the onset, which was sudden and without warning. Lumbar puncture and subsequent spinal fluid examination confirmed the diagnosis, a high protein reading being a significant feature. Toxic encephalopathy is certainly the

INTENSIVE ARSENOTHERAPY OF EARLY SYPHILIS

menace of intensive arsenotherapy. Our cases occurred later in treatment than is usually described.

Agranulocytosis.—This occurred in 3 patients, in 2 cases on the twenty-third day and in one on the twenty-fourth, after receiving 730, 1,130 and 960 milligrams of mapharside respectively. Sore throat and gums heralded the onset; pyrexia, headache, malaise and other symptoms soon followed. Treatment with mapharside was immediately discontinued and Pentide (sodium pentose nucleotide) was given. All the patients recovered and subsequently completed their treatment with bismuth.

Vincent's angina.—We had 5 cases of gingivitis due to Vincent's angina. We mention this merely to show, as others have done, that Vincent's angina can occur in spite of a patient being saturated with arsenic.

Arsenical dermatitis.—Two mild cases occurred, one on the eighteenth day and one on the twenty-fifth. Arsenical treatment was stopped and both patients completed their treatment with bismuth.

Jaundice.—We have had 4 cases occurring during treatment and 16 cases occurring after completion of treatment. Of these, 3 patients subsequently completed their treatment after a break of a few days.

Relapse and reinfection

Out of a total of 241 cases treated, we have had 21 relapses (giving a percentage of 8.7) and 10 reinfections.

Incidence of relapse in each category

"Early primary"	{	total number of cases	...	...	70
		number of relapses	...	...	2
"Middle primary"	{	total number of cases	...	...	37
		number of relapses	...	...	1
"Late primary" (including secondary)	{	total number of cases	...	...	134
		number of relapses	...	...	18

Of the relapses in the "late primary" category, 16 occurred before the introduction of bismuth, out of a total of 72 cases; 2 only have occurred in 62 cases since the introduction of bismuth.

The duration of surveillance of the above 241 cases has been from a minimum of 9 months to a maximum of 2 years.

Incidence of reinfection in each category

"Early primary"	4
"Middle primary"	1
"Late primary" (including secondary)	5

We feel that there is little doubt as to the authenticity of the above figures but, owing to present conditions and the exigencies of the Service, it is quite impossible for surveillance to be anything like complete. Our figures must be considered accordingly as a minimum of the relapse and reinfection incidence.

Summary

A re-categorization of so-called early syphilis is presented. It is based on the quantitative serum test for syphilis and, according to the degree of intensity of infection as shown by this test, we have been able to classify 3 groups, namely, "early", "middle" and "late" primary syphilis. This is considered to be a decided advance in the diagnosis of early syphilis and should help, in answer to Moore's statement quoted above, in the solution of the problem of determining which types of cases can be probably cured or aborted by small amounts of treatment, as opposed to the predetermined fixed dosage now being used for early syphilis irrespective of the stage of the disease.

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DISCUSSION ON THE PRECEDING PAPER

Brig. Osmond (the President) asked whether the incubation period of jaundice among the cases under discussion was anything like the ninety-day period of the cases of jaundice in the Army.

Lt.-col. King expressed some doubt as to whether the difference between 15 and 20 daily injections of Mapharside was a matter which greatly increased or diminished the risk to the patient. On the question of jaundice he noticed that Cdr. Maitland had had some cases of jaundice occurring during intensive treatment and others at a later stage. The evidence was that there were two types of jaundice which commonly occurred in the treatment of syphilis with arsphenamines. The type which occurred early appeared to be associated with the syndrome known as "erythema of the ninth day"; the later jaundice, with a definite incubation period, seemed to be due to a syringe transmission.

Lt.-col. Lees said that his experience of intensive arsenotherapy was limited to about 100 cases in Cairo, where the five-day technique was used. He had been uneasy about the results; one patient died, 3 nearly died and a bulbar syndrome developed in another; the experiment was dropped.

Maj. Marshall said that he had tried to work out an intensive method of treating out-patients with arsenic along the lines suggested by Eagle and Hogan. Treating a dozen patients in that way had not been successful. He gave mapharside 3 times a week to women out-patients, and without exception they had very severe toxic dermal reactions on about the ninth day. So severe were the effects of the treatment that it had to be suspended and only two or three patients could be desensitized sufficiently for the treatment to be carried to a conclusion within a reasonable time; in others it had to be suspended entirely.

Sqn.-ldr. Jean Morton said that she had used intensive treatment with mapharside in an 8-day to 9-day scheme planned on the Eagle and Hogan method. The main point about the treatment with mapharside was the question of discipline in the ward and the necessity for a very good nursing service. It did not rest so much with the medical officer as with the nursing staff, who must make very accurate observations.

Over 100 women had been treated, 50 of whom had completed 6 months of observation. Out of that number there was one case of encephalopathy, which was not fatal. In this woman, who weighed 105 pounds, encephalopathy developed after she had had 1,190 milligrams; 6 months later her tests were negative. Quite a number had a rash or a general reaction. Any increase in the patient's temperature was of importance. The temperature readings were made 4-hourly and recorded in a special book. A patient with a temperature of 99° F. after an injection should be watched carefully. Persistent headache was also a very important symptom; but the nurses told her that the most important factor was the girl's behaviour; if a patient became gloomy, rather irritable and did not look well, it was an indication that she was becoming intolerant to arsenic. Sqn.-ldr. Morton had not had any cases of jaundice either during or after treatment.

Of the 50 cases which had completed 6 months' observation after treatment, 3 had relapsed serologically and one of them showed a mucocutaneous relapse. Most of the patients were very well during treatment, gained in weight and after treatment looked extremely fit. On the whole she thought that it was a satisfactory method of treatment.

Dr. W. N. Mascal wished to bear out Maj. Marshall's observations as to intensive arsenical therapy. He had tried to use an intensive course for out-patients, giving injections of Neo-halarsine 3 times a week over a period of 12 weeks. Some of the results were good, but the completion of the treatment had been interfered with more by defaulting than by any therapeutic complications, particularly among young women. In a group of 20 cases only 2 had completed the 12 weeks' treatment; in 2 cases jaundice developed. He felt that the experiment had been a failure.

Dr. C. P. Heywood said that he had had some experience with the intensive arsenical treatment of syphilis in Newcastle-upon-Tyne. A 20-day course of treatment was given to all cases diagnosed as primary syphilis, but unfortunately some were found to be really cases of early secondary syphilis; serological relapses were experienced very quickly and the ordinary routine treatment was now being given to these patients. The 20-day intensive course was now used for the early primary cases only; for the late primary and the secondary cases a 30-day course was introduced. This treatment, in the patients who could tolerate it, had been entirely successful during the short observation period. In cases in which severe reactions occurred these were apt to appear on the tenth day. Experience in desensitizing such patients had been a complete