AMBULATORY TREATMENT OF EARLY SYPHILITIC INFECTION

AMBULATORY TREATMENT OF EARLY SYPHILITIC INFECTION WITH PENICILLIN*

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It is possible that the treatment of syphilis with arsenic may, in the near future, be a thing of the past, its place being taken by penicillin. The first series of penicillin-treated cases was described by Mahoney, Arnold and Harris in December 1943.

Four cases were quoted, and all have been kept under observation since that date. They were all cases of early syphilis and showed dark-field positive lesions. Treatment consisted of intramuscular injections, into the buttock, of 25,000 units given at four-hourly intervals day and night to a total of 48 injections; the total amount of penicillin given was 1,200,000 units. Of these cases 3 attained sero-negativity within 3 months and showed rapid healing of the clinical lesions. The fourth patient's lesion healed rapidly; his reactions became sero-negative on the 71st day and remained negative for a further 210 days, when they became serologically strongly positive. He was at that time under treatment for specific urethritis. When examined, it was found that he had a single ulcer with an indurated base on the inner surface of the lower lip and enlargement of the regional lymph glands. On dark-ground examination *Spirochaeta pallida* was demonstrated from the ulcer. There was no other evidence of skin or mucous membrane involvement. Because of doubt this patient, although most probably a case of re-infection, was classed as a treatment failure.

Since then Mahoney (with Arnold, Sterner, Harris and Zwally) has published a further series of 100 cases, all likewise treated with 1,200,000 units.

Of these cases 52 became available for evaluation after an arbitrary minimum of 75 days' surveillance, although the average is 135 days; 30 of these cases were so-called dark-field positive primary syphilis cases, and 6 of them were stated to be consistently sero-negative during treatment. "There is a possibility of there being 27 satisfactory responses" in these 30 cases. "Of the remaining 22 patients, who displayed evidence of secondary syphilis, and who were well into the seropositive phase of the disease at the time of treatment, 11 have progressed to seronegativity or have displayed a consistently satisfactory trend in that direction." In their comments on these cases the authors quoted make the important statements that "very early infections respond in the most favourable manner", and that "the increase in probable failures in patients with secondary syphilis indicates the need of a more vigorous therapy".

Moore, Mahoney, Schwartz, Sternberg and Wood have published a series of 1,418 cases of early syphilis treated with penicillin, 663 of them with penicillin alone. The majority of these have been observed only for less than 2 months; only a total of 113 cases have been observed for 4 months or longer. The following is a summary of the results and findings of these cases.

All cases were treated by intramuscular injections every 3 hours day and night for 60 injections covering 7½ days; the total dosage varied from 60,000 to 1,200,000 units. Disappearance of *S. pallida* from surface lesions varied according to the dosage, from 21 hours in a 1,000-unit dose to 14 hours with a 40,000-unit dose. Duration of healing of lesions in cases treated with 300,000 units or over was in the same ratio as with standard chemotherapy. The positive serological response, regardless of the total dosage, began to show reversal about 20 days after commencement of treatment, depending upon the initial titre; the response of those cases treated within a range of 300,000 to 1,200,000 units was approximately uniform, but with a total dosage of 60,000 units it was a little slower and less pronounced. Of 48 patients who started with a negative serological reading, 28 cases remained so throughout this period of observation, 18 cases became temporarily positive, then reverted to negative, and in 2 only was there a subsequent serological relapse. "From the serological standpoint, therefore, . . . the results may be said to be satisfactory in 95·8 per cent of the cases."

In seropositive early syphilis (including secondary syphilis) "there is a direct relationship . . . between serological response and total dosage of penicillin: the larger the dose, the better the response". Thus, of 38 cases treated with 60,000 units total dosage, there was an unsatisfactory serological response in 42·1 per cent. Of 62 cases treated with 1,200,000 units total dosage, the unsatisfactory serological response dropped to 9·6 per cent.

The total incidence of relapse, clinical and serological, in all types of early syphilis observed for more than 38 days, was again in direct proportion to total dosage used. With 60,000

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units it was nearly 29.6 per cent and with 1,200,000 units only 2 per cent, showing direct correlation between total dosage and relapse incidence.

These findings must lead to the opinion that the only available criterion of the minimum effective dose of penicillin in early syphilis to date lies in the incidence of relapse, clinical and serological.

In Moore's series there were 25 cases only treated by various intravenous methods, that is, repeated intravenous injections and intravenous drip. These methods were considered to be less effective than the intramuscular route and the relapse rate appeared to be higher. It is emphasized by Moore and his fellow authors (and we should like to stress this) that "the eventual use" of penicillin "for the civil community depends on the development of methods which will permit its administration on an ambulatory basis".

Concerning the question of treatment, Moore has raised an important point, in suggesting that "600,000 units of penicillin in a total dosage given concurrently with a sub-curative dose of mapharsen, 40 milligrams daily for 8 days, totalling 320 milligrams, is apparently equal in therapeutic efficiency to 1,200,000 units of penicillin given by itself". He has also recently stated that the present relapse rate after total dosage of 1,200,000 units of penicillin was about 15 per cent and would rise probably to about 20 per cent as the ultimate relapse rate (Moore). With double the dosage, 2,400,000 units, the relapse rate was about equal, and an increase of dosage did not appear to be a hopeful line of investigation. Results on a small group indicate that the relapse rate after a course consisting of 40 milligrams a day of Phenarsine Hydrochloride (U.S.A. proprietary, 3-amino-4-hydroxyphenyldichlorarsine hydrochloride) and 300,000 units of penicillin for 8 days was lower than that for either penicillin or arsenic alone, and there was some evidence that the effect of the two medicaments might be more than additive.

The lines proposed for investigation were therefore not to increase the dosage of penicillin alone, but first to spread out the same dosage over a longer course and secondly, to investigate the effects of giving penicillin and arsenic together.

TABLE 1—RESULTS OF TREATMENT WITH SINGLE DAILY INTRAVENOUS INJECTIONS OF PENICILLIN

Total dosage in the course	1.2 to 2.4 million units	2.4 to 5 million units	
Single daily intravenous injection	300,000 units	300,000 units	500,000 units
Toxic effects :			
Herxheimer reaction	3	4	2
Pyrexia over 100°F.	3	1	1
Headache and shivering	10	16	9
Venous thrombosis	4	1	1
Vasomotor reaction	3	4	—
Results :			
Wassermann test negative (in weeks)			
(a) Late primary	7.0	6.7	6.5
(b) Secondary	12.7	10.0	11.0
Relapse	2	1	1
Re-infection	1	—	—
Disappearance of <i>S. pallida</i> (in hours)	10.0	8.9	9.0
Surveillance :			
Under 3 months	7	8	10
Over 3 months	18	14	8
Total number of cases 65	25	22	18

This synergistic action is worth evaluating and further results may warrant a trial of such a method. Is there not, however, the grave risk of converting an

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absolutely safe therapeutic procedure into a possibly dangerous one? A daily small dose of mapharsen or of Phenarsine Hydrochloride is suggested, but no mention is made of the possible risk of toxic encephalopathy and other toxic results which often accompany daily injections of arsenic. We know that this may happen with even the smallest dose of arsenic given daily, and at an early stage of treatment. The 3 cases of toxic encephalopathy in our own series of intensive arsenotherapy occurred on the 9th, 10th and 12th days of treatment, after only 400, 400 and 440 milligrams of mapharsen respectively.

The need for simplification of treatment

The methods of treatment carried out to date, that is to say, three-hourly to four-hourly intramuscular injections, intravenous drip and intramuscular drip, have one factor in common, namely the necessity of sending the patient into hospital. In the Forces special hospitals or wards are generally available for the treatment of venereal diseases; these are equipped with the necessary means for penicillin or arsenic control, they are staffed by trained personnel and, most important of all, there is an adequate number of beds for the accommodation of patients. For the general community, however, such luxuries are not available, and therefore civil cases have for the most part to be treated as out-patients, essentially on an ambulatory basis. Even if beds were available, few of the civil population, men or women, either could or would give up from 7½ to 10 days to go into hospital; they cannot afford the time. The multiple injection schedule is exacting in time and work for the staff. It is, in the main, and particularly with certain brands of penicillin, uncomfortable or painful and disturbing for the patient; his rest is upset and there is always the possibility of an abscess developing at the site of injection to add to his boredom and discomfort.

It is essential, therefore, that some alternative scheme of treatment be found. Penicillin is, after all, a new non-toxic substance and it is surely permissible to try to evolve any method of treatment which may eventually prove to be successful. We have, in the recent advances in syphilis treatment, been more or less dependent upon work done in the United States of America. Intensive arsenotherapy has shown this clearly and now the pioneer work with penicillin follows. Possibly we in Great Britain are too conservative in this respect but, whatever the cause may be, we should not allow it to prevent progress.

Present investigations

We began the treatment of syphilis with penicillin in mid-June 1944, using the repeated intramuscular method. Our initial total dosage was 1,200,000 units, this being raised later to 2,400,000 units, as had been recommended, and we continued with this form of treatment for 2 months.

During that period it struck us very forcibly that this type of treatment for syphilis, necessitating complete confinement to hospital until the total number of injections had been given, had serious drawbacks and difficulties, even in the Forces.

We felt that in order to cope with these difficulties any efficient method which did not involve in-patient treatment, and which was applicable to the Forces and the general community alike, would be of the utmost benefit. This important aspect was uppermost in our minds in evolving what we have reason to believe is a practical solution to these problems. Why should it be necessary to keep a patient in hospital, away from his work and duty, for a non-debilitating disease? Unquestionably the ideal form of treatment would be one involving at the most a single daily injection and given on an out-patient basis.

The single daily intravenous dose

In August 1944, working on this idea, we began by trying out what single daily dose, given intravenously, would fulfil our expectations and achieve similar results to those of the established repeated intramuscular method. We had no indication whatsoever as to what single minimum intravenous dose would be required to

eliminate *S. pallida* from surface lesions, nor had we any idea as to what maximum dose a patient would tolerate in the form of a single injection given intravenously. Fortunately, with penicillin the practical problems of treatment and the reactions to treatment do not assume the same proportions as they do with arsenic. As far as is known, penicillin itself is completely non-toxic, so that large doses may be given without any fear of agranulocytosis, toxic encephalopathy or other serious complications, provided that the prescriber is familiar with the characteristics of any specified brand of penicillin—and this is important. It is correct to state that very large single or total doses may be given without any fear of reaction. A warning, however, must be given, and this is repeated below, that certain brands, although they are perfectly safe in the customary small dose, may cause reactions if given in the large single intravenous doses described below; care should therefore be exercised in their use for this purpose.

SERUM

1 in 256
1 in 128
1 in 64
1 in 32
1 in 16
1 in 8
1 in 4
1 in 2
1 in 1

FIG. 1—SERUM INHIBITION LEVEL AFTER SINGLE INTRAVENOUS INJECTION OF PENICILLIN

Serum = Serum dilutions inhibiting growth of *Staphylococcus aureus*.

500,000 units 3 minutes after injection gave a serum dilution inhibiting growth of 1 in 4096.

300,000 units 3 minutes after injection gave a serum dilution inhibiting growth of 1 in 2048.

160,000 units 3 minutes after injection gave a serum dilution inhibiting growth of 1 in 1024.

(In the above graph only the half-hourly dilutions have been plotted.)

Experiments were carried out before we came to any definite and practical decisions, by giving single intravenous injections of penicillin of the following amounts: 40,000, 80,000, 120,000 and 160,000 units. In each category we made the following determinations.

- (1) The minimum time taken for the disappearance of *S. pallida* from surface lesions and their subsequent absence for 24 hours.
- (2) Blood serum penicillin content at half-hourly intervals.
- (3) Maximum time taken for elimination of penicillin in the urine.

It was found that all amounts below 160,000 units were inconsistent in their spirochaeticidal effects, but with 160,000 units consistent results were obtained. *S. pallida* disappeared from surface lesions in an average of 11 hours and were still absent 24 hours later; penicillin was present in the blood up to 5 hours and in the urine up to 16 hours. As a result of these experiments we had established the fact that a single intravenous dose of 160,000 units of penicillin was capable of removing spirochaetes from surface lesions in an average of 11 hours and, moreover, that they were still absent 24 hours later. It was not considered necessary to control *S. pallida* for longer than this period, and in comparison with a routine dose of an arsenical compound the spirochaetes were removed in half the usual time.

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Reference to other work showed that a total dosage of 2,400,000 units had been suggested as necessary for the cure of early syphilis in order to prevent a high relapse incidence. This total dosage, then, would require 15 days with the use of a single daily dose of 160,000 units; therefore, in order to come into line with the already existing eight-day period of treatment, we decided to increase our single intravenous dose to 300,000 units daily for 8 days. Would our patients tolerate this dose? We were most fortunate in using a non-toxic brand of penicillin at the time, and the immediate and subsequent reactions to this dose, apart from some primary rise in temperature and slight headache, were precisely nil.

Results obtained.—With this dosage spirochaetes were removed from surface lesions in an average of 9 hours; penicillin was excreted in the urine up to 17 hours and shown to be present in the blood up to 6½ hours. Although the blood serum content in no way compares with the constant serum penicillin level obtained with the four-hourly intramuscular method, the resultant spirochaeticidal effect was indeed excellent.

Subsequently we treated a number of cases with a single daily 500,000-unit injection with no untoward effects whatsoever. Experiments with this dosage showed again that spirochaetes were absent from surface lesions in an average of 9 hours, but the blood penicillin level showed a rise up to 8 hours and its excretion in the urine was detected up to 23 hours. This may, perhaps, satisfy those who are desirous of maintaining a constant concentration of penicillin in the body in between injections, for this length of time of excretion in the urine leads us to the opinion that penicillin must be present in the blood for a period longer than 8 hours, although the amount, presumably, is too minute to be detected by our present laboratory methods.

Estimation of results.—It has been the opinion up to now that a definite concentration of a chemotherapeutic agent, such as the sulphonamides, must be maintained in the blood stream in order to ensure successful results. This supposition has also been taken to be essential by those who are now using penicillin; it has become a *sine qua non*. As judged by clinical results, this supposition has not however been shown to be always necessarily applicable. It is probably because this constant blood level was looked on as a necessity that repeated intramuscular injections and continuous drip methods were adopted initially for the treatment of syphilis with penicillin.

As judged by the survey of our cases treated by this intravenous method up to date, covering a period of up to 6 months' surveillance, a consistently high serum inhibition content over a period of 24 hours has not been proved to be essential. Surely the treatment of any disease must be judged by practical results.

Methods and safeguards

Laboratory check for potency of penicillin.—It is our practice to test each new batch for therapeutic potency and unitage by the inhibition of *Staphylococcus aureus* (Oxford strain) as described by Fleming. Periodical checks are made also to ensure concentration of penicillin in the solution in use, and so forth. This also helps to keep the staff keen and to eliminate a possible human error. The expiry date on the bottles can be exceeded safely if this is done but, even without such testing, a latitude in time of up to 3 months beyond the date may be regarded as safe, if storage has been satisfactory.

Solutions for use.—As a vehicle for the solution of penicillin, sterile distilled water, sterile Apyrogen water, sterile physiological saline and sterile 5 per cent glucose may all be used; no differences in their use have been observed by us.

Sterilization.—Owing to the inhibiting effects of antiseptics, sterilization of syringes and needles must be done by means of heat, such as boiling or dry heat, or by oil sterilization at 140°C. All syringes used in treating our series of cases have been sterilized by boiling between injections. For cleaning the top of the penicillin bottle and the skin, we have used ether, but methylated spirit evaporates so rapidly that in practice it also can be used with safety. In discussing sterilization, the subject of jaundice inevitably comes to mind. We have had one case, which

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occurred approximately 8 weeks after treatment with 3,000,000 units. As far as we could ascertain, there was no history of recent exposure to any other source of infection, in fact there was no aetiological history of anything suggestive. Clinically the condition was typical of those cases which occur after arsenotherapy.

Categorization and penicillin therapy

The different categories and appropriate treatment of each with penicillin have not been stressed in the same way as has been done when intensive arsenotherapy was under discussion (Jones and Maitland). There are two reasons for this.

(1) We feel that there is not the same necessity for re-categorizing types or groups of "early syphilis" which are undergoing treatment with penicillin,

TABLE 2—RESULTS OF TREATMENT WITH MULTIPLE INTRAMUSCULAR INJECTIONS OF PENICILLIN

Total dosage in the course	1·2 to 2·4 million units	2·4 to 5 million units
Multiple 3-hourly injections of	40,000 units	40,000 units
Toxic effects :		
Herxheimer... ..	2	—
Pyrexia over 100°F.	2	—
Headache and shivering	15	4
Vasomotor reaction	—	—
Results :		
Wassermann test negative (in weeks)		
(a) Late primary	7·2	10·0
(b) Secondary	14·0	—
Relapse	—	—
Re-infection	1	—
Disappearance of <i>S. pallida</i> (in hours)	10·1	10·0
Surveillance :		
Under 3 months	5	—
Over 3 months	26	4
Total number of cases : 35	31	4

because surplus dosage does not come into the question nor assume the same dangerous significance as when arsenic is used. Penicillin is a completely non-toxic and harmless substance, whereas, in dealing with arsenic, the different categories were evolved not only to show the different types of "early syphilis" but also with the idea of regulating the amount of arsenic necessary for the treatment of each type, in order to eliminate as far as possible the dangers which are associated with a fixed pre-determined dose of a toxic substance.

(2) We are still feeling our way in this new technique. We have found, however, comparing the single intravenous with the multiple intramuscular method, that the "early primary" cases continue to be consistently sero-negative during treatment, the "middle primary" cases still show their temporary positive phase, and the "late primary" are more or less identical in their behaviour as regards the time taken for the titre to fall, as estimated by the quantitative serological test for syphilis.

Dosage and categorization.—As we had re-categorized "early syphilis" cases

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receiving intensive arsenotherapy, we continued to categorize our cases and to administer doses of penicillin empirically in order to try and establish the relative category dosage required for the three different groups. We realize, indeed, that it is difficult to perform daily blood tests for categorization purposes, but if blood tests are made on the 1st, 4th 7th and 10th days respectively from the commencement of treatment, this will give a fairly reliable guide as to the category. However, by means of our categorization we hope to evolve some mean dosage which will be suitable for all types of early syphilis treated where facilities are not available for categorization purposes. The only true estimate of dosage must be one based on the relapse incidence. As yet it has not been possible to judge the correct doses, owing to smallness of numbers treated and inadequate length of surveillance. Dosage can be determined only by adequate and careful surveillance or, in other words, records of trial and error.

Decrease in Wassermann titre

In all our cases (with the exception of one patient, who relapsed clinically before the titre had fallen, and one who, we think, had become re-infected before the titre had dropped) the fall from sero-positive to sero-negative has been most satisfactory and has occurred, on an average, in 7 weeks after the commencement of treatment in the "late primary" group and 11.2 weeks in the "secondary" group. Once down to negative they have remained so consistently, and this compares most favourably with the titre drop in our intensive arsenotherapy cases (Jones and Maitland). It is this reversion to the negative which gives the necessary encouragement to persevere with the single daily intravenous injection. In some cases the fall has been sudden; as a general rule, however, it occurs more gradually, the graph of its fall resembling the temperature fall by lysis of an acute fever (see Figs. 1 and 2).

Reactions

With a selected brand of penicillin, apart from the primary reaction, these are negligible. In our series there has not been any necessity to suspend or alter treatment in any case on account of toxic reactions. However, with certain brands of penicillin care must be taken as definite reactions may occur. The following reactions have been noticed to date.

(1) One patient had a rather alarming collapse after receiving 500,000 units intravenously of a brand with which we were not familiar. Fortunately this state lasted only a few minutes and he then quickly recovered, but it was our first indication that care was necessary. That brand has not been used since for large single daily intravenous injections, although it has proved to be entirely satisfactory for intramuscular injections of from 10,000 to 30,000 units.

(2) Another reaction, which may be troublesome if certain brands are used, is venous thrombosis. This seems to occur up to or about 48 hours after the injection, and in certain patients' arms would unquestionably be most inconvenient. This was overcome by adding heparin, 1,000 to 1,500 units per 300,000-unit or 500,000-unit injection; clotting and bleeding times were measured and found not to be altered sufficiently to be of any practical significance. With this same brand of penicillin, unpleasant vasomotor reactions were remarked on by the patients during or immediately after the injection. Flushing, faintness, sweating, pain in the arm along the course of the vein and a nasty taste in the mouth were common. The addition of heparin seemed also to neutralize these to some extent. A taste of "pear drops" is usual with the large intravenous doses.

(3) One patient who received this same brand, and who had a childhood history of asthma and eczema, had a violent urticarial reaction about $\frac{1}{2}$ hour after the injection, but on the next day, when a different brand of penicillin was used, no reaction occurred.

(4) The pain which occurs after intramuscular injections, again, is a variable factor and depends largely upon the brand of penicillin used.

All these reactions may be attributed to the impurities or pyrogens or both present in the penicillin extract and are dependent upon the process of manufacture.

How can the kind of penicillin which is going to give these reactions be detected? This is usually a case for experiment, but the colour of the prepared solution is a good general guide; the lighter the colour the less likely is the occurrence of toxic reactions. The brand we have found to be most suitable gives only a faint straw colour in solution.

FIG. 2—REACTIONS OF PATIENTS TREATED WITH PENICILLIN

Single dose, 500,000 units.
Total dosage, 4,000,000 units.

Single dose, 300,000 units.
Total dosage, 2,400,000 units.

W.R. = Wassermann reaction blood titre, recorded in months

T. = Temperature, recorded in days

L.P. = Late primary syphilis

Both cases were treated with single daily intravenous injections of penicillin. Case 58 received 500,000 units per injection and Case 28 received 300,000 units.

The Primary Reaction.—Pyrexia, headache, shivering and occasionally nausea have occurred in 65 cases in the series. This syndrome does not appear to represent a true Herxheimer reaction, as there is rarely any exacerbation of existing signs and, on this account, there seems to be little risk in using our scheme of dosage in conditions in which a Herxheimer reaction is usually to be feared. The primary reaction may occur with any dose, and is not confined to the large single injection. The patient is uncomfortable for a day, but it does not worry him if he is warned beforehand of the likelihood; rest in bed and aspirin soon make him comfortable. The next day he is perfectly well and continues treatment without interruption. Out-patients should always be warned about this primary reaction.

Relapses and re-infections

So far, out of our series of 146 cases treated with penicillin, mostly by single daily intravenous injection, there have been 4 relapses (3 clinical and 1 serological). They occurred from 7 weeks to 15 weeks after completion of treatment. One of them was an early primary case, sero-negative throughout the initial treatment period and up to the time of relapse; but as the fresh sore occurred at the site of the original lesion, and as the man most strongly denied any re-exposure to infection, the lesion must be classified as a relapse. These relapsed cases have all received further treatment with penicillin and are reacting favourably.

So far 2 re-infections have occurred.

The first patient became re-infected while his serum titre was still relatively high, 2 weeks after receiving 2,400,000 units, given three-hourly in intramuscular doses of 40,000 units, for "late primary" syphilis. His fresh sore was not on the original site, a later stage of syphilis had not developed and *S. pallida* were demonstrated from the fresh sore. His papers showed that he had been successfully treated for syphilis previously in 1939. Such infection, occurring during a still positive phase of the blood, is believed to be possible, and it has been suggested by Schoch and Alexander as happening after intensive arsenotherapy, so that there is no reason to doubt the possibility of its occurrence after penicillin treatment. This patient's wife was examined after his fresh marital exposure by a very competent observer, and she was found to have secondary syphilis.

The second re-infection was reported 7½ weeks after initial treatment (2,400,000 units given by single daily intravenous injections of 300,000 units) for a "middle primary" type of syphilis. The patient had had sexual relations with his wife 2 weeks after completion of treatment. The fresh sore was not on the original site, spirochaetes were present, and

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Wassermann and Kahn tests were negative at the time of re-infection. His wife too was examined by the above-mentioned observer, who again diagnosed secondary syphilis. These, to us, are two conclusive cases of re-infection, both after treatment with 2,400,000 units of penicillin, the first after multiple three-hourly injections of 40,000 units given intramuscularly, and the second after 8 single daily intravenous injections of 300,000 units.

Cerebrospinal fluid examination

As in the case of intensive arsenotherapy, this examination is performed on every patient before he leaves the hospital, and in our series to date all results have been entirely negative. In all, 24 cases have been re-examined after 4 months' surveillance and again found to be negative.

It has been stated that penicillin does not reach the cerebrospinal fluid. As a matter of interest, we have found this to be so by testing the cerebrospinal fluid inhibition one hour after giving intravenous doses of 300,000 and 500,000 units to patients who had no signs of symptomatic neurological involvement. Recently, with the cooperation of Surg.-Cdr. Ross, R.N.V.R., we have examined the cerebrospinal fluid of 2 patients with general paralysis of the insane, who were treated with single doses of 300,000 and 500,000 units respectively. In both these cases no trace of penicillin was found in the cerebrospinal fluid one hour later.

Summary of results obtained

We have had under treatment a total of 146 cases in which *S. pallida* were demonstrated. Unfortunately 44 of our cases have not had sufficient surveillance for evaluation purposes. This leaves a total of 102 cases fulfilling surveillance requirements.

Of these, 65 have been treated by the single daily intravenous injection method (see Table 1), 35 by the multiple daily intramuscular method (see Table 2), and 2 by the single daily intramuscular method. They were placed in the following categories: "early primary", 18; "middle primary", 13; "late primary" (including secondary), 71. (See Table 3.) Out of this total of 102 cases there have been 4 relapses, one in the "early primary" group and 3 in the "late primary" group. This gives a relapse rate of 3.9 per cent in a total of 102 cases. These 4 relapse cases all occurred after treatment by the single daily intravenous method, which may cause some concern in assessing the relative value of the single daily intravenous method as compared with the repeated intramuscular method; but if the comparative value of the two methods is to be judged solely by our relapse incidence, it should be appreciated that almost double the number of cases were treated by the intravenous method.

Of the 102 cases treated, 36 have been under surveillance less than 3 months, and 66 from 3 to 8 months. Of the 4 relapse cases, 2 occurred at 9 weeks, one at 7 weeks and one at 15 weeks after completion of penicillin therapy. There have been two re-infections; both were exposed to infection from their wives 2 weeks after completion of treatment.

The 35 cases in Table 2, treated by the multiple daily intramuscular method, were given an average of 2,400,000 units of penicillin. The 65 cases in Table 1, treated by the single daily intravenous method, have had a total dosage varying from 2,400,000 to 5,000,000 units. Of these 14 were "early primary" and had a mean dosage of 2,400,000 units; 4 were

TABLE 3—SUMMARY OF PENICILLIN-TREATED CASES

Cases of syphilis		Kind of injections		
		Single daily		Multiple 3-hourly
Category	Total number of cases	Intravenous	Intramuscular	Intramuscular
Early primary	18	14	—	4
Middle primary	13	5	—	8
Late primary	55	35	1	19
Secondary	16	11	1	4
Totals	102	65	2	35

"middle primary", 2 of whom had 2,400,000, one had 3,000,000 and one had 5,000,000 units. There were 47 "late primary" and secondary cases; 15 of these had 2,400,000, 11 had 3,000,000, 13 had 4,000,000 and 7 had 5,000,000 units. The 2 cases treated by the single daily intramuscular method each had a total of 2,400,000 units.

Of the total of 4 cases which relapsed, 2 had had 2,400,000 and 2 had had more than 2,400,000 units.

With regard to the drop in the Kolmer-Wassermann titre, it appears that no definite relation exists between total dosage and the average time taken for the reversion of a positive blood reaction to negative; wide variations occur, which may be anything from 2 to 20 weeks; this is our finding for both the intramuscular and intravenous methods.

An alternative to the intravenous route

In September 1944, 2 cases (referred to above) were given single daily intramuscular injections of 300,000 units for 8 days, each case receiving a total of 2,400,000 units; *S. pallida* disappeared in 9 and 12½ hours respectively. Both cases ("late primary") responded well to this form of treatment, and have been under surveillance for 5 and 6 months respectively. Unfortunately, no further cases were treated in this manner at the time but, on the suggestion of Sir Alexander Fleming, we have lately carried out further work on similar lines and 20 cases have been treated to date. As a comparison with the intravenous method, the spirochaetes tend to disappear in the same ratio of time in regard to dosage. With a 300,000-unit dosage, given intramuscularly, the blood content of penicillin is prolonged from 7 to 11½ hours and the urine content prolonged from 17 to 23 hours; with a 500,000-unit dosage the blood content of penicillin is prolonged from 8 to 13 hours and the urine content from 24 to 25 hours.

These 20 cases are under surveillance at the present time and no definite conclusions as to the final results can as yet be made, but, judging by their satisfactory trend of progress to date and by the results of the two cases already described, this alternative method of treatment, in our opinion, merits further investigation; we feel, at the moment, that there is no reason to doubt its efficiency as compared with the single daily intravenous method of treatment.

The occurrence of first-day pyrexia in this method of treatment is much less marked and less frequent than is the case with the intravenous method. As a general rule no pain or discomfort has been noted and no untoward incidents have occurred.

Out-patient treatment

The single daily intravenous or intramuscular method of injection can be an out-patient form of treatment from the start. Several of our cases are already being treated in this manner.

We believe that penicillin will shortly be available in sufficient quantities to satisfy all requirements, and if it becomes the drug of choice for syphilis and if the single daily intravenous or intramuscular method is adopted, the ever-present bugbear of the scarcity or absence of beds will be done away with and the sociological and allied problems associated with in-patient treatment will be solved. This method will enable all persons suffering from syphilis to be given the advantage of this medicament which, under existing methods of treatment, is denied them; it should be the solution to Moore's statement quoted above, that "the eventual use" of penicillin "for the civil community depends on the development of methods which will permit its administration on an ambulatory basis".

We suggest this method of treatment as a solution to the present problems in the administration of penicillin. If it is found that this method of large single daily intravenous or intramuscular injections is satisfactory, as judged by adequate surveillance, by the incidence of relapse, and by what are considered to be other satisfactory criteria for cure, then some advance in the treatment of syphilis with penicillin will have been achieved.

We wish to thank the Medical Director General, Sir Sheldon Dudley, for his cooperation and his encouragement to carry out this work, Sir Alexander Fleming for the kindly advice

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and help he has always given us, and the Sick Berth staff for their never-failing help and collaboration.

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DISCUSSION ON THE PRECEDING PAPERS

Brig. Osmond (the President) said that the two papers were some of the most interesting to which the Society had listened for a considerable time, and that he was glad to be the first to congratulate the two officers on the result which they had achieved. He was particularly interested in Surg. Lt. Cdr. Maitland's explanation of the results in his cases. He had never been quite convinced by the usual explanation of the Herxheimer reaction, and Cdr. Maitland's explanation might be the right one. As a point of interest, he would add that in the Army intensive treatment had been given in a much greater number of sero-negative primary than of sero-positive primary and secondary cases.

With regard to encephalopathy, Ransome (in a paper not yet published) had stated that the nursing of patients in Fowler's position gave much better results than those obtained in the lying-down position.

As regards relapse rates, penicillin seemed to compare extremely well with intensive arsenic. Brig. Osmond thought that great care must be taken in diagnosing re-infections, because the more he thought about it, the more inclined he was to call the condition a relapse unless there was clear evidence of re-infection. As regards future therapy, such conditions should be treated as relapses.

If he might prophesy, it would be to say that most venereologists in the future would be using bismuth as well as intensive arsenic or penicillin. Penicillin acted in the same way as did the old "606", by knocking out 99 per cent of the spirochaetes, but bismuth dealt with the odd 1 per cent. Toxic reactions were nearly all due to impurities, and if penicillin were made more pure there would probably not be any toxic reactions. It was said that penicillin did not get into the cerebrospinal fluid, but it was carried to the brain and nerve tissues by the blood stream and might be expected to act nearly as well in cerebrospinal syphilis as in somatic syphilis.

With regard to the single daily dose method mentioned by Surg. Capt. Lloyd Jones, the facts that penicillin remained in the body so much longer when given in large doses, and that patients could be treated on an out-patient basis, were very encouraging.

Lt.-col. A. J. King said that he had listened with particular interest to the account of methods attempted in order to overcome the difficulties attendant upon the use of penicillin for the treatment of syphilis by multiple injection. He took it that the speakers would not regard this as more than a preliminary report; the whole investigation would be much more interesting and convincing if presented after a lapse of a year or two.

With regard to Cdr. Maitland's point about the three stages of primary syphilis and the suggestion that upon these should depend the amount of treatment given, the suggestion was interesting. Personally, however, he did not feel convinced, because this method seemed to leave out of consideration the personal idiosyncrasy of the patient and his ability to use the drug. It had always been the principle in the case of a disease such as syphilis to over-treat rather than under-treat; he thought, in view of the serious late manifestations, that it was a disease in which a little extra treatment might act as an insurance.

The President had raised a point regarding re-infections. It seemed clear to most people that recurring syphilis must be regarded as relapse until it was established by the most stringent criteria as re-infection.

Finally Col. King thought that the necessity for treating syphilis on an ambulant basis in civil life was being exaggerated. If the patient had a respiratory infection, influenza or a severe cold, he had in most cases no difficulty in taking a week away from his work; in the case of a serious disease like syphilis, it seemed to him that it was purely a matter of education to convince the public as a whole that it was essential for that length of time away from work to be allowed if there was the chance of cure of so serious a condition within a short time.

Col. L. W. Harrison said that he had found the papers very provocative; he hoped that the authors would not think him too conservative if he criticized them a little. The idea of giving a single daily injection was most important; if it proved to be successful, it would solve many practical difficulties. The Ministry of Health had recently issued a circular in which the treatment recommended for syphilis included 60 injections of penicillin at 3-hourly intervals; he would watch for the results of the single daily dose method with interest and sympathy, but for the present he proposed to adhere to the multiple daily injection procedure.

On the question of re-infections, he agreed with the President and Col. King as to the danger of diagnosing as re-infections what were in fact relapses. During, or just after, the war of 1914-