OUT-PATIENT TREATMENT OF EARLY SYPHILIS WITH PENICILLIN

A SURVEY OF 215 CASES TREATED BY SINGLE DAILY INJECTIONS

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Penicillin treatment of syphilis now ranks as one of the great medical advances of the war; the saving of man-hours already achieved has justified its adoption for the routine treatment of early syphilis in the armed Forces, although the end-results have yet to be evaluated. The original plans of treatment, which aim at the maintenance of relatively constant levels of penicillin in the blood over an arbitrary minimum period of 8 days, provide the basis for the majority of treatment schedules in current use. Such treatment, calling as it does for frequently repeated intramuscular injections, necessitates admission of the patient to hospital.

When penicillin became available for the treatment of syphilis in the Royal Navy it was considered important to evolve as quickly as possible an ambulatory method which would be applicable to the majority of patients in widely scattered ships and establishments. With this end in view an investigation was inaugurated in June, 1944; and in March, 1945, a preliminary report was made by one of us (T. R. L.-J.) in the form of an address to the Medical Society for the Study of Venereal Diseases. Two series of cases were described, the results of an ambulatory method calling for single daily intravenous injections comparing favourably with those of a multiple (three-hourly) injection method on conventional lines.

The present contribution reports the condition of the 100 cases originally treated (Lloyd-Jones and Maitland, 1945) after further observation, and describes an additional series of 150 cases treated by daily intramuscular injections and investigations directed to defining time-dose relationships. It is not considered useful at the present time to submit detailed clinical and statistical reports on this material.

Scheme of Investigation*

The results previously obtained with daily intravenous injections supported the view that a constant level of penicillin in the blood stream was not a necessary condition for cure. We felt encouraged, therefore, to continue our work on intermittent penicillin therapy and, on the suggestion of Prof. Sir Alexander Fleming, decided to treat a series of cases by daily intramuscular injections. In order to secure a basis for comparison with previous series we restricted treatment to cases of freshly acquired syphilis—primary or secondary. For the purpose of description we refer to primary cases of syphilis as "early," "middle," or "late": the early cases being those which remain sero-negative throughout; the middle primary cases those which are sero-negative at the start of treatment, show a short positive phase, and return to negative about the end of treatment; and the late primary cases those which are sero-positive at the outset (Lloyd-Jones and Maitland, 1943).

On the assumption that the total amount of treatment required for "cure" is related to the age of a syphilitic infection, we proceeded to modify the time-dose relationship within these categories, in the light of results observed as the investigation progressed. The manipulation of the separate factors involved will be apparent as the various series are discussed. Under Service conditions it was not felt justifiable to adhere strictly to a predetermined dosage scheme as would be done in a controlled experiment: the interest of the individual demanded modification of the schemes as relapses occurred. Later we carried the investigation to its logical conclusion by progressively decreasing the number of days' treatment, the total dose of penicillin remaining approximately constant.

* American commercial brands of sodium penicillin were used throughout.

Management of Cases

All cases here reported have had a minimum of three months' surveillance; several have been observed for periods up to fifteen months. Routine surveillance comprises weekly clinical examinations and quantitative Kolmer-Wassermann tests until sero-negativity has been attained or, in cases originally sero-negative, over a period of three to four months after treatment. Thereafter monthly examinations and blood tests are carried out. Cerebrospinal fluid examinations are made at the beginning of treatment and at the end of four months. So far as is possible cases are retained under our personal supervision until after the second cerebrospinal fluid examination.

Clinical Results

Immediate response was similar with all schemes of treatment—spirochaetes disappearing, lesions healing, and reversal of serology occurring within the same time limits. It is worthy of note that spirochaetes disappeared from surface lesions in the average time of nine hours after single injections ranging from 160,000 to 6,000,000 units. Sero-relapse occurred in five cases; all other relapses shown in the tables are examples of early infectious relapse, occurring as a rule between two and four months after treatment.

It should be realized that it is not our purpose to enlarge on detailed clinical results, pending the evolution of a fixed dosage scheme and its clinical trial on a larger number of cases. Furthermore, final evaluation must obviously await the passage of the years.

First Series (Three-hourly Intramuscular Method).—Table I brings up to date the previous report on the original series of 35 cases treated in 1944 and requires no further comment.

TABLE I.—*Series Treated by Three-hourly Intramuscular Injections*

No. of Cases	Total Dose of Penicillin	Method	Relapses
4	1.2 mega units	15,000 × 3-hourly	Nil
4	1.6 " "	20,000 " "	"
27	2.4 " "	40,000 " "	"
Surveillance			{ More than 1 year .. 9 cases " 9 months .. 11 " " 6 " .. 12 " " 3 " .. 3 "

Second Series (Daily Intravenous Method).—The second series comprises the cases already reported (Lloyd-Jones and Maitland, 1945) with the addition of cases which have now fulfilled surveillance requirements. Results are shown in Table II.

TABLE II.—*Series (102 Cases) Treated by Single Daily Intravenous Injections*

No. of Cases	Category	Daily Dose of Penicillin in Units (Single Injection)	No. of Days' Treatment	Total Amount of Penicillin given in Mega Units	Relapses
9	Early primary	300,000	8	2.4	1
3		300,000	10	3.0	Nil
3		300,000	8	2.4	"
4	Middle primary	300,000	10	3.0	"
1		300,000	13	3.9	"
14		300,000	8	2.4	2
9	Late primary	300,000	10	3.0	Nil
2		300,000	11	3.3	"
17		300,000	13	3.9	1
3	Secondary	300,000	8	2.4	Nil
3		300,000	10	3.0	1
10		300,000	13	3.9	2
78					7 (9%)
3	Early primary	500,000	5	2.5	Nil
2		500,000	7	3.5	"
1		500,000	7	3.5	"
1	Middle primary	500,000	10	5.0	"
1		500,000	5	2.5	1
1		500,000	7	3.5	Nil
3	Late primary	500,000	8	4.0	"
7		500,000	10	5.0	"
1		500,000	7	3.5	"
4	Secondary	500,000	10	5.0	"
		500,000	10	5.0	"
24					1 (4.2%)

Surveillance		{ More than 10 months .. 19 cases " 8 " .. 38 " " 6 " .. 21 " " 3 " .. 24 "
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In order to provide a basis for comparison with the conventional three-hourly intramuscular method employed in the first series it was decided to administer the same total dosage of penicillin (2,400,000 units) over the same time-period (eight days). This necessitated a single daily injection of 300,000 units. The total dosage was then increased in the light of results observed as the series progressed, but as the daily injection was kept constant it was spread over a greater number of days. To offset this increase in time-spread the daily injection was increased to 500,000 units in the later cases. Table II indicates that results remained satisfactory when the time under treatment was reduced in this way, and the larger daily injection offers obvious advantages in the smaller number of injections required to complete treatment.

Third Series (Daily Intramuscular Method).—Table III summarizes the results in this, the third series treated.

TABLE III.—*Series (113 Cases) Treated by Single Daily Intramuscular Injections*

No. of Cases	Category	Daily Dose of Penicillin in Units (Single Injection)	No. of Days' Treatment	Total Amount of Penicillin given in Mega Units	Relapses
24	Early primary	300,000	8	2.4	1
7		300,000	10	3.0	Nil
5	Middle primary	300,000	8	2.4	"
5		300,000	10	3.0	"
1	Late primary	300,000	13	3.9	Nil
2		300,000	10	3.0	"
38	Secondary	300,000	13	3.9	"
18		300,000	13	3.9	2
9		300,000	15	4.5	Nil
109					6 (5.5%)
1	Middle primary	500,000	8	4.0	Nil
3		500,000	8	4.0	"
4					Nil
Surveillance ..		More than 7 months ..			14 cases
		" 5 " ..			47 "
		" 3 " ..			52 "

On the basis of the results shown in the tables we tentatively suggest as minimum dosage schemes for these methods:

300,000 Unit Dose			
Primary	Early ..	10 single daily injections of 300,000 units	= 3.0 mega units
	Middle ..	12 " "	" = 3.6 "
	Late ..	13 " "	" = 3.9 "
Secondary ..	15 " "	" "	" = 4.5 "

From the point of view of treatment the separation of cases into categories can no longer be regarded as essential, and when facilities for frequent quantitative serological tests are not available, early, middle, and late primary may be regarded as a single group—primary syphilis—and given the dosage recommended for the late primary group.

500,000 Unit Dose

Primary syphilis: 8 daily injections of 500,000 units, giving a total dosage of 4 mega units.
Secondary syphilis: 10 daily injections of 500,000 units, giving a total dosage of 5 mega units.

This method has now been temporarily adopted for routine use, but to date only a few cases satisfy our surveillance requirements.

Technique.—The unitage of penicillin required was dissolved in 2–3 ml. of sterile water and injected intramuscularly into the buttock. The injection was repeated daily, alternating between the left and right sides, until the total dosage had been given.

TABLE IV.—*Intensive Treatment (30 Cases)*

No. of Cases	Individual Dose of Penicillin	Total Amount of Penicillin given	Time-spread of Treatment	No. of Relapses	Average Time to Relapse	Relapses (%)
6	1 mega unit	5 mega units	5 days	3	10 wks.	50
10	1 " "	4 " "	4 " "	5	7.2 "	50
2	1 " "	3 " "	3 " "	1	8 "	50
4	Variable, up to 3 mega units	5 " "	2 " "	3	10 "	75
4		5 " "	Up to 3 hrs.	4	5.7 "	100
1	5 mega units	7 " "	3 hrs.	1	8 "	100
3	5 mega units	5 " "	1 injec.	3	4.1 "	100

No reaction of any moment was seen and in no case did treatment have to be interrupted or suspended. Primary reactions following the first injection did occur, but constituted no bar to out-patient treatment.

In view of the encouraging results in the earlier series we decided to investigate further the time-dose relationship by progressively decreasing the time-spread while keeping the total dosage at or above the amount we regarded as curative in the previous series. These were cases of primary syphilis, and all were kept under strict supervision, with careful examination bi-weekly. It is evident from Table IV that a dose (5 mega units) which would be curative when spread over ten days, as in the third series, already described, is inconsistent in its results when this time-spread is reduced to five days or less. Moreover, there is a suggestion that as the period of treatment is reduced the relapses tend to occur at shorter intervals after treatment.

These results may be compared with those of Lourie *et al.* (1945), who have reported three cases given six doses of 200,000 units daily for two days—a total of 2.4 mega units—with ineffective results; and a further two cases of secondary syphilis treated for four days—one with 4.8 mega units, the other with 9.6 mega units—both with satisfactory results. They have also treated 17 cases with a total dosage of 9 mega units spread over five days, and all have so far proved highly successful.

Syphilis Acquired Concomitantly with Gonorrhoea

Ten patients apparently contracted syphilis at the time they were infected with gonorrhoea. All had been treated with penicillin for the latter disease—one case receiving 800,000 units (single injection), another 300,000 units (single injection), the remainder 150,000 units in five injections of 30,000 units. All developed primary lesions within the limits regarded as normal for the incubation period of syphilis. It is interesting to note that in none of these cases had the relatively high doses employed in any sense "masked" syphilis.

Neurosyphilis

Only cases of early syphilis have been reported above, but in addition to these we have treated 10 cases of "asymptomatic neurosyphilis" by single daily injections until a total dosage varying from 2.4 to 5 mega units had been administered. The cerebrospinal fluid of four of these cases reverted to normal within six weeks, and although the cerebrospinal fluid of the remaining six has shown definite improvement, mainly in cell content and globulin and protein estimations, they have not become normal so far.

Penetration of Penicillin to the C.S.F.—An interesting sidelight on the above results is provided by the report of Lourie *et al.* (1945), who demonstrated small amounts of penicillin in the cerebrospinal fluid of the rabbit and of man after relatively large parenteral injections. We have carried out three similar experiments on cases of primary syphilis with no signs of meningitis: (1) a patient to whom we gave a single dose of five million units intramuscularly showed no trace of penicillin in the cerebrospinal fluid at one or at two hours after the injection; (2) a patient to whom we gave a single dose of six million units intramuscularly showed no trace of penicillin at three hours, but at four hours a slight amount was present; (3) a patient to whom a single dose of six million units was given intramuscularly showed a penicillin concentration of 0.125 unit per ml. at five hours and also the same amount—0.125 unit per ml.—at six hours after injection. These results suggest that higher dosages of penicillin than those hitherto employed may be given with advantage to cases of neurosyphilis. They also lend support to the plea (Ross *et al.*, 1944; Lourie *et al.*, 1945) for the routine use of larger doses in all forms of syphilis.

Discussion

We have described methods of treatment for early syphilis suitable for use in out-patients. These are based on the hypothesis that a sustained and relatively constant blood level of penicillin is not a necessary condition for cure. When the investigations were started no laboratory evidence was available to confirm or refute this hypothesis, but the recent work of Lourie *et al.* (1945) may now be cited in its favour. Working *in vitro* with *Spirochaeta recurrentis*, they found that 99% of the

organisms were rendered non-viable in eight hours by a penicillin concentration of 0.62 unit per ml., and that with higher concentrations the same effect was produced in a shorter time—e.g., in a concentration of 10 units per ml. 99% were non-viable after two hours.

Optimum time-dose relationship has always been a crucial factor in the chemotherapy of syphilis. There is as yet no agreement on the optimum relationship in the case of penicillin, but we believe we have made some contribution to the eventual solution of this problem, our results indicating that a time-spread of five days or less is inadequate even with our relatively enormous total doses.

However, as penicillin becomes more abundant it seems desirable that routine dosage should greatly exceed minimum requirements, especially as there appears to be little danger of overdosage. The low incidence of primary reactions following initiation of treatment in our cases is in accord with the experience of Lourie *et al.* (1945). Indeed, it seems that the higher the initial dose the fewer and less severe are the reactions following it; this observation may have important applications in the management of cases in which it is imperative to minimize therapeutic shock effects.

We have not investigated the possible advantages of combined penicillin and arsenic or bismuth therapy, as it appeared to us desirable first to determine the results to be expected with penicillin alone.

Results with our scheme of "intermittent penicillin therapy" have been encouraging, but are not intended for direct comparison with those reported for multiple-injection methods by other workers. Such comparisons must await the results of large-scale trials, which we believe are now justified, and in fact daily-injection methods have now been approved for more general use in the Royal Navy.

Although sodium penicillin has been used throughout this work, we have to state that calcium penicillin, made available to us by Surg. Cmdr. C. A. Green, R.N.V.R. (R.N. Medical School, Clevedon), is now under investigation; results to date compare favourably with those reported above for the sodium salt.

Summary

An out-patient scheme for the treatment of early syphilis with sodium penicillin, supported by a report on 215 cases, is presented.

The system of treatment consists of daily injections of an aqueous solution, and is based on the hypothesis that a continuous level of penicillin in the blood stream is not a necessary condition for cure. Intravenous and intramuscular routes are equally effective, but the latter is preferred on grounds of convenience.

Investigations relative to time-dose relationships are reported.

Penicillin has been demonstrated in the cerebrospinal fluid, in the absence of meningitis, following parenteral injection.

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In Poland, as in all liberated countries, professional men are eagerly demanding opportunities to catch up with the lost years, to make good the blanks in professional studies caused by the Nazi occupation. In particular, doctors are impatient to receive information about the advances made by medical science during the years 1939-46. To meet this demand, Dr. Wilbur Sawyer, Chief of U.N.R.R.A. Health Division in Washington, made a tour of Poland last autumn, lecturing on influenza, yellow fever, and insect vector control. His tour was so successful that U.N.R.R.A. has sent further specialists in different branches of medicine to make a similar tour. From Britain Dr. N. H. Martin has lectured on nutrition, and Dr. Marc Daniels is giving a series of lectures on tuberculosis and is also making a tuberculosis survey of Poland. Another American, Dr. Nevitt, has instructed Polish doctors on the latest technique of plastics in dentistry. Russian authorities on physiology and tuberculosis will probably visit Poland in the near future.

A CASE OF PERIARTERITIS NODOSA THE ROLE OF ANAPHYLAXIS

BY

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Periarteritis nodosa is a disease of obscure origin, rather rare but of great clinical and pathological interest. Only the severe forms can be recognized clinically, and recovery is relatively infrequent. The vessels affected are usually of the size of the hepatic artery or smaller. There is necrobiosis, followed by leucocytic infiltration, exudation, and subsequent development of granulation tissue. Some authors prefer the term "necrosing arteritis" to periarteritis nodosa, as the lesion is not always nodose. It is my intention to discuss a case in the light of the observations made by Rich (1942). I believe that every case of periarteritis nodosa deserves special attention, as it is often difficult to diagnose and as the study of the aetiology and pathogenesis of the disease (or perhaps it is better to say "syndrome") may throw more light on the obscure aetiology of certain other diseases, such as ulcerative colitis.

Case Report

Miss A., aged 42, was admitted to this hospital on Feb. 17, 1943, complaining of general malaise and pain in the joints preceded by a "rash" on both legs of three weeks' duration. With the exception of a chronic duodenal ulcer from which the patient was presumed to suffer, there was nothing of interest in her past history. On examination she looked ill and apathetic. The temperature was 102.6°, the tongue furred, the abdomen distended, and there were a few rales at the base of the right lung.

On Feb. 20 the patient developed an urticarial rash, which persisted for several days. She also complained of weakness and pain in the legs and had difficulty in moving the feet. A few days later the pain in the legs became rather severe, and the sluggish knee-jerks, together with the dropped feet, suggested peripheral neuritis of both legs.

On Feb. 25, seven days after admission, the patient suddenly complained of severe abdominal pain. The abdomen was tense and tender, the pulse rapid, perspiration was excessive, and she vomited rather copiously. Surgical intervention was discussed, but was postponed. She was much improved three days later. Her condition, nevertheless, seemed worse after a short time. The pyrexia persisted, as well as the neuritis. She became very wasted and incontinent of urine, and diarrhoea was a prominent feature.

The following investigations were carried out during her stay in hospital:—Blood count (Feb. 22): Red blood corpuscles, 4,300,000 per c.mm.; haemoglobin, 75%; colour index, 0.87; white blood cells, 19,800 per c.mm. (polymorph neutrophils, 90.5%; eosinophils, 1.0%; basophils, 0.5%; large mononuclears, 6.5%; metamyelocytes, 1.5%). Agglutination tests of serum for enteric fevers and brucellosis were negative on Feb. 26 and April 2. No pathogenic coliform organisms were found in the faeces. Urine examination revealed pus and epithelial cells in small numbers, a few red blood corpuscles, and a trace of protein. Casts and crystals were not seen, and there was no growth on culture. Radiographs of the chest revealed localized pleural thickening in the right costo-phrenic angle.

The patient did not respond to chemotherapy and there was no improvement in the condition of the legs with vitamin B treatment. She died in the middle of May (about three months after admission) with no definite diagnosis. The various diagnoses suspected were: in the early stages, *infective polyneuritis*; in the later stages, *abdominal Hodgkin's disease*.

Appearance of organs at necropsy: (1) Nodular swellings 0.5 cm. in diameter along course of coronary arteries; (2) fine nodular enlargement along mesenteric arterioles; (3) numerous infarcts in kidneys; (4) thickening of arterioles in liver and spleen; (5) acute ulcers in stomach, duodenum, jejunum, and ileum; (6) acute fibrinous pericarditis. Histological examination showed: chronic polyarteritis nodosa in liver, spleen, suprarenals, pancreas, stomach, ileum, and mesentery. The axillary and radial arteries were normal.

Discussion

It is worth noting that this case (in spite of great difficulties in diagnosis) is in reality almost "classical" of periarteritis nodosa as described in most of the textbooks. The urticarial rash and pain in the joints mentioned above are certainly of great interest, and it is important to insist on this particular point of the clinical picture, as not only may it be a help in suspecting periarteritis nodosa in an obscure case of such