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PENICILLIN IN NEUROSYPHILIS*

BY

C. WORSTER-DROUGHT, M.A., M.D., F.R.C.P.

Physician, West End Hospital for Nervous Diseases and Metropolitan Hospital

General Observations

Penicillin, introduced into therapeutics in 1941, was at first restricted to the treatment of certain specified infections. This limitation was by Government direction, and was mainly due to the necessity for conserving the somewhat scanty supplies. It is only within the last year that penicillin has become available for more general use, and especially for experimental therapeutics. Nevertheless, penicillin already has an established place in the treatment of neurosyphilis. It was recognized quite early that the substance had a definite antispirochaetal action, and in 1943 Mahoney, Arnold, and Harris published the results of treating a series of cases of early syphilis with penicillin. From these and the subsequent observations of other workers it became apparent that the immediate results of treatment with penicillin in early syphilis equalled if they did not exceed those obtained with intensive arsenical and bismuth therapy. Further, there was the added advantage that with penicillin there was little or no risk of toxic reactions. Subsequently, rapid improvement in both the clinical condition and the cerebrospinal fluid changes in various forms of late syphilis was reported.

From the follow-up of cases of early syphilis treated with penicillin alone, however, it became apparent that a moderately high rate of relapse occurred. In addition, it was noted that the percentage of cases relapsing was roughly inversely proportional to the total dosage of penicillin given; in the earlier cases treated this had no doubt been inadequate. These observations finally determined what was considered an optimal total dosage expressed in so many Oxford (now international) units. By June, 1944, penicillin was adopted as the "drug of choice" for the treatment of early syphilis in the U.S. Army in Europe, and, in the autumn of 1944, in the Royal Navy, R.A.F., and the British Army. The standard course was fixed at a total dosage of 2,400,000 units given in doses of 40,000 units every three hours, day and night (60 injections), over a period of seven and a half days. Even with this dosage the average relapse rate in early syphilis appears to have been as high as 15% in some series of cases (Marshall, 1946; King, 1946), while others report an 8% (Marshall, 1946) and 7% (Moore, 1945) relapse rate.

Dosage and Methods of Administration

Most of the present-day experiences of penicillin in neurosyphilis are based on the results of a dosage and a frequency of administration similar to those of the standard course referred to above. From subsequent variations of dosage, however, it is clear that we still have much to learn in order to evolve the most satisfactory method of applying penicillin, especially in the treatment of neurosyphilis.

Many authorities have considered it advisable, if not essential, that the concentration of penicillin in the blood should be kept at as high a continuous level as possible throughout the period of treatment. It was found that penicillin disappeared from the blood after four hours from the time of injection. The level of penicillin in the blood therefore could be kept up either by a continuous drip technique or by an intravenous, intramuscular, or subcutaneous injection given every three hours, the average period of treatment required to reach an adequate total dosage being seven and a half to eight days.

Intravenous penicillin therapy has little to commend it. The continuous drip technique is inconvenient, troublesome, and needs special apparatus, while even with repeated single intravenous injections there is a risk of thrombophlebitis (Kolodny and Denhoff, 1946). On the other hand, three-hourly intramuscular injections of penicillin in adequate doses yield equally good if not better clinical results than those following intravenous treatment. Thus, according to Mahoney and his co-workers (1944), relapse was more frequent after penicillin treatment given by intravenous injection (including continuous intravenous drip) than by repeated intramuscular injection.

The recent tendency is towards the administration of a somewhat larger total dosage of penicillin in neurosyphilis. Several authors (e.g., Olansky and Chinn, 1946; Marshall, 1946) advocate a total dosage of 4,000,000 units given in repeated intramuscular doses of 40,000 units every three hours.

Some authors consider that it may not be necessary to keep a measurable level of penicillin in the blood constantly throughout the period of treatment, but that equally good therapeutic effects might be obtained by administering much larger doses at considerably longer intervals—for example, twenty-four hours—until an adequate total dosage is reached. Thus Lloyd-Jones and Maitland (1945) state that single doses of from 300,000 to 500,000 units given daily for eight to fourteen days yield equivalent therapeutic results to those following the usual standard course—namely, 60 injections of 40,000 units given every three hours—although no trace of penicillin can be detected in the blood twelve hours after the massive injection.

I have treated some cases of meningovascular neurosyphilis by this method, giving a daily dose of 500,000 units of penicillin intramuscularly for 14 days, and agree that the immediate clinical response is good. It is far too early,

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however, to judge the ultimate results; should these prove satisfactory when cases have been followed up for sufficiently long periods, the problem of treating cases of chronic neurosyphilis in out-patient departments, instead of admitting them to hospital as at present, would largely be solved. If it is eventually shown that a continuous and fairly constant level of penicillin in the blood is really necessary for full therapeutic effects, the preparations of penicillin in oil and beeswax may prove valuable—for example, injectio penicillin. oleosa, *B.P.*

I have invariably used sodium penicillin in watery solution for injection by all routes and have no personal experience of oil–wax preparations. Harrison (1946), who has been using these preparations, states that after a deep subcutaneous injection of 300,000 units in oil–wax, penicillin can be found in the blood serum for 12 to 16 hours but not at the end of 24 hours. Similarly, Kirby, Leifer, and their co-workers (1946) found that an injection of 300,000 units of highly purified calcium penicillin (of potency 1,000 units per mg. in 1 ml. of peanut oil with 4.8% of beeswax) given by subcutaneous injection maintains an assayable blood level of penicillin for 20 hours. Thus patients can be treated with one injection daily of 300,000 units in oil–wax for 10 to 14 days (total dosage of 3,000,000 to 4,200,000 units). From these observations it would appear that, if the maintenance of a fairly constant concentration of penicillin in the blood throughout the period of treatment proves to be necessary, the use of oil–wax preparations is the method of choice for daily injection in out-patient cases of neurosyphilis. If such a continuous level in the blood should not be necessary, however, then watery or saline solutions of penicillin are preferable, for I am aware that examples of persistence of the oily preparation in the tissues (non-absorption) have been reported, and occasionally a localized and tender induration appears three days after injection of the oil–wax penicillin (Pillsbury, 1945).

Penicillin Combined with Arsenicals and Bismuth

In view of the percentage of relapses reported in cases even of early syphilis treated with penicillin alone, and in spite of the initial beneficial effects following penicillin treatment, I have at no time abandoned the use of arsenicals and bismuth—in conjunction with penicillin—in treating cases of neurosyphilis. It is of interest to note that many authors (e.g., Marshall, 1946; McElligott, 1946; Olansky and Chinn, 1946) advocate the combined use of penicillin, arsenicals, and bismuth not only in neurosyphilis but also in early syphilis. It is even possible that a synergistic action exists between the two types of treatment as indicated by the animal experiments of Eagle and his co-workers (1946) and the observations of Levaditi and Vaisman (1946).

Using the standard course of penicillin administered parenterally, the most appropriate method of applying the combined treatment is to give three injections of arsenic and bismuth during the week of penicillin treatment in order to utilize the possible synergistic action (in doses of 0.3 g. of neoarsphenamine and 0.2 g. of bismuth). The course of penicillin is then followed up by 12 injections of an arsenical—0.45 g. of neoarsphenamine or 0.06 g. of "mapharsen" ("mapharside")—and bismuth (0.2 g.) at weekly intervals. Some observers prefer to give the arsenical and bismuth every four days for forty days—10 injections of each substance—using 0.45 g. of neoarsphenamine, 0.06 g. of mapharsen, or 0.09 g. of "neohalarsen," given intravenously, and 0.2 g. of bismuth intramuscularly (McElligott, 1946).

It will not be possible fully to assess the final results of penicillin treatment—even when combined with the older methods—for several years. A careful and prolonged follow-up of cases is imperative. We can only wait and ascertain what proportion of the thousands of cases of early syphilis treated with penicillin alone in the British and U.S. Forces will eventually relapse or develop some form of neurosyphilis. Consequently, as a result of further observations, it may be necessary to amplify, extend, or otherwise alter the schemes of treatment at present in use.

Intrathecal Administration of Penicillin

However advisable in acute meningeal infections such as streptococcal and pneumococcal meningitis, is the intrathecal injection of penicillin either indicated or advisable in neurosyphilis—or can equally good therapeutic results be obtained by parenteral injection alone?

The evidence as to whether penicillin given by parenteral injection is able to penetrate the blood–brain barrier (choroid plexus) into the subarachnoid space has been somewhat contradictory. Thus it is stated that penicillin injected parenterally in standard doses does not reach the cerebrospinal fluid in demonstrable quantities (Marshall, 1946). McDermott and Nelson (1945) found only traces of penicillin in the cerebrospinal fluid after the intramuscular injection of a single dose of 300,000 units or over (which produced a blood concentration of penicillin of 10 units or more per ml.). On the other hand, Schwemlein and his co-workers (1946) claim that penicillin injected parenterally reaches the cerebrospinal fluid in adequate amounts. There is more recent evidence that massive single doses of penicillin—for example, 600,000 units given every hour—may penetrate the blood–brain barrier in larger quantities (Lourie *et al.*, 1945; Lloyd-Jones, Allen, and Donaldson, 1946; Schwemlein *et al.*, 1946).

It is considered by some observers (e.g., Rosenberg and Sylvester, 1944; Dickson Wright, 1946) that if the choroid plexus is damaged by inflammation—for instance, in meningitis—penicillin may reach the cerebrospinal fluid in somewhat larger quantities than normally.

Is it necessary for penicillin to pass the blood–brain barrier in order to exert an adequate therapeutic effect in neurosyphilis (including parenchymatous neurosyphilis)? My answer is "No," since adequate clinical response, with rapid reduction in cell and protein content of the cerebrospinal fluid towards normal, is obtainable in most, if not all, cases of meningovascular neurosyphilis treated by parenteral injections of penicillin; and, further, in forms of parenchymatous neurosyphilis (general paresis and tabes dorsalis) considerable improvement in the pathological cell content and total protein of the cerebrospinal fluid is observed in many cases—as well as a slower decrease in the intensity of the serological reactions. Consequently, whether or not penicillin passes the blood–brain barrier in "adequate" amounts, it is certainly capable of exerting considerable effect on the meninges and central nervous system when given by parenteral injection. In view of these facts it is probable that the reaction between the infecting organism and the antibiotic takes place mainly in the leptomeninges, these membranes being well supplied with blood vessels. In my earlier cases of neurosyphilis treated with penicillin I used the intrathecal route, giving 10,000 units in 10 ml. of normal saline by lumbar puncture every day for eight to ten days, at the same time administering the usual standard penicillin treatment by intramuscular injection (40,000 units every three hours for seven and a half to eight days). I was fortunate in meeting with no excessively severe reactions—as judged by certain published reports, to which I will refer later—but there is often a brisk meningeal reaction accompanied by some pyrexia and generalized pain after the first intrathecal injection. The cerebrospinal fluid drawn off by lumbar puncture on

the following day will be found to contain a larger number of cells (varying from 500 to 10,000 per c.mm. and including a high percentage of polymorphs) and an increased total protein of from 80 to 250 mg. per 100 ml. The pleocytosis persists, but with diminishing intensity, throughout the course of intrathecal penicillin. In tabes dorsalis the initial intrathecal injections may provoke a severe attack of "lightning pains."

As a result of further observation and experience with parenteral injections I have now abandoned routine intrathecal injection of penicillin in neurosyphilis, preferring intramuscular injection in adequate dosage, except for certain cases of tabes dorsalis with severe and frequent "lightning pains."

If intrathecal injection is decided upon it is best to give 10,000 units of penicillin in 10 ml. of saline daily by lumbar puncture, more than this quantity of cerebrospinal fluid having been drawn off, and to repeat the injection for seven to ten days. (In acute streptococcal and pneumococcal meningitis intrathecal penicillin may be necessary at intervals of 12 hours for the first three or four days.) It has been shown (Cairns *et al.*, 1944) that a single intrathecal dose of 4,000 units maintains an adequate level of penicillin in the cerebrospinal fluid for 24 hours. Penicillin appears in the lumbar cerebrospinal fluid after an intraventricular injection, and administration by lumbar puncture gives rise to a substantial concentration in the cerebrospinal fluid bathing the brain and even in the ventricular fluid. Cooke and Goldring (1945), however, advance the view that the presence of large amounts of penicillin in the cerebrospinal fluid after lumbar intrathecal injection suggests stasis to be the reason for such high concentration, whereas the presence of large amounts of penicillin in the intraventricular fluid suggests that the blood stream may be the source of the penicillin, as the direction of the flow of the cerebrospinal fluid is from the ventricles to the subarachnoid space.

The introduction of penicillin by cisternal puncture in neurosyphilis seems to be not only inadvisable but hazardous according to the results of Neymann, Heilbrunn, and Youmans (1945). These authors report muscular twitchings and generalized convulsions in cases of general paresis, as well as two deaths from what they term "chronic penicillin encephalopathy" following the injection of penicillin by the cisternal route. Lesions of the cauda equina following the injection of penicillin by lumbar puncture have been described, and convulsions have resulted from intraventricular injections (Smith, Duthie, and Cairns, 1946). Also, the American *Year Book of Neurology and Psychiatry*, 1946, refers to motor weakness, optic atrophy, bladder incontinence, neuroradiculitis, mental abnormalities, and cerebral atrophy occurring after the intrathecal and intraventricular administration of penicillin (Siegal, 1945; Walker and Johnson, 1945; Sweet, Stanley, *et al.*, 1945). Some of these effects may have been due to impurities in the penicillin used, as earlier preparations of penicillin issued were considerably less pure than those now available.

Therapeutic Reactions

All observers testify to the relative harmlessness of penicillin compared with its unexampled destructive effect on many bacteria. By rapid intravenous injection the penicillin concentration of the blood can be forced up to a level 1,000 times greater than is necessary to produce therapeutic effects without untoward incident (Fleming, Young, Suchet, and Rowe, 1944). Even in early syphilis, however, some 50% of cases treated with penicillin experience varying degrees of malaise and usually slight pyrexia after the initial doses (McElligott, 1946). A few individuals may be sensitive to some constituent of the penicillin. Generalized urticaria, with or without constitutional disturbance, has occasionally been observed one week or so after the first injection, but it is not an indication for discontinuing treatment (Pillsbury, 1945). Only very few instances of more severe systemic reactions, including profound malaise, continued pyrexia, and toxicodermal reactions, have been reported (Kolodny and Denhoff, 1946). There is no recorded instance of any damaging effect on bone marrow, liver, or other organs. With the more recent, and purer, preparations of penicillin such reactions are less frequent; consequently, the earlier reactions recorded were probably due to impurities. Calcium penicillin is said to be six times more toxic than sodium penicillin, but even this is negligible, as the lethal dose in a man weighing 60 kg. would seem to be over 10,000,000 units (Welch, Chandler, Davis, and Price, 1945).

Herxheimer-Jarisch reactions have been reported from time to time in cases of neurosyphilis in addition to other forms of late syphilis, as well as in early syphilis, treated by penicillin alone. Personally, I have observed no more than a pyrexial reaction following the first or second dose of penicillin (given intramuscularly), and very occasionally some discomfort in the legs with temporarily increased spasticity in cases of meningomyelitis. To judge from some of the published reports, however, it would seem that I have been fortunate, as various forms of exacerbation of symptoms, including thrombosis, have been observed, and even acute transverse myelitis (McElligott, 1946). In view of the possibility of Herxheimer-Jarisch reactions following penicillin injection, however, I now prefer to give six injections of bismuth (0.5 ml. of "bismostab") every four days in meningovascular neurosyphilis, and four injections of bismuth at the same intervals in parenchymatous neurosyphilis, before proceeding with the full course of penicillin.

Meningovascular Neurosyphilis

There is abundant evidence that penicillin—in adequate dosage and administered by whatever route—has a striking initial beneficial effect on all forms of meningovascular neurosyphilis, especially acute forms. The therapeutic effect is observed not only in the tendency to subsidence of clinical symptoms but more particularly in the rapid improvement in pathological cerebrospinal fluids. The pleocytosis and the increased protein content will often show a noteworthy decrease within a few days of starting treatment and reach a normal level within two to four weeks. The intensity of the Wassermann reaction (and other serological reactions) in the cerebrospinal fluid gradually decreases and may become negative within two to four months. These results suggest an actual selective action of penicillin on pathological cerebrospinal fluids or meninges, as there is no parallel decrease in the serological reactions of the blood. The blood Wassermann reaction may continue positive for many months, and even indefinitely, after treatment limited to penicillin.

The clinical response of syphilitic meningitis to penicillin (by parenteral injection) is usually immediate and dramatic. In acute forms of the disorder headache and neck rigidity may disappear within 48 to 56 hours, and the increased cell and total protein content of the cerebrospinal fluid rapidly reaches a normal level. The serological response, as stated previously, is somewhat slower. Cranial nerve palsies improve gradually and usually recover. Nelson and Duncan (1944) mention five cases of syphilitic meningitis with cranial nerve palsies, all of which made a good recovery with penicillin treatment, the cranial nerve lesions disappearing completely in four cases. In the remaining case some residual weakness was still present after 98 days.

From the observations of Stokes and his co-workers (1944 to 1946) it is doubtful if any further change towards improvement occurs after four months from the termination of penicillin treatment. Consequently these authors have thought it advisable to repeat the course of penicillin after this four-month interval. At the time of reporting, however, they had noted no conspicuous benefit as a result of repeating the course. Repetition is advocated by other observers: for example, two courses of penicillin of a total dosage of 2,400,000 units at a week's interval (Marshall, 1946) and the usual course of penicillin at intervals of three weeks for two or more courses (McElligott, 1946). Further time must elapse before the value of such repeated courses can be finally assessed.

As stated previously, in most cases of neurosyphilis (especially parenchymatous forms) the serological reactions in the blood—particularly the Wassermann reaction—are little affected by penicillin treatment and will often continue to show positive results long after the cerebrospinal fluid has become normal. This observation may furnish a further argument for following up the course of penicillin with arsenical–bismuth therapy; also relapse may occur in a cerebrospinal fluid that has become normal as a result of penicillin treatment although a return to the original pre-treatment severity is unusual.

Parenchymatous Neurosyphilis

Even in parenchymatous forms of neurosyphilis, such as general paresis (G.P.I.), the initial effect of penicillin treatment—injected by whatever route—on the symptomatology (usually) and upon the cerebrospinal fluid changes is remarkably good. In cases of early general paresis treated with penicillin alone I have seen the cell and protein content of the cerebrospinal fluid become normal within four weeks, and even a strongly positive Wassermann reaction becomes negative within two months; the blood Wassermann reaction continued strongly positive. Six months later, however, the Wassermann reaction in the cerebrospinal fluid may be found weakly positive, the blood Wassermann reaction still remaining strongly positive. These later results determined me to combine penicillin treatment with the usual course of fever therapy—for example, malaria, 10–12 rigors—in all cases of general paresis; and in tabes dorsalis to follow up the penicillin treatment with full arsenical and bismuth therapy.

(a) General Paresis

Some authors claim definite clinical improvement in cases of general paresis treated by penicillin alone. As judged by the literature, however, most observers now use penicillin in combination with either the usual arsenicals, "tryparsamide," bismuth, or some form of pyrexial therapy for the treatment of this condition. The results reported are somewhat conflicting. All observers agree, however, that even when penicillin alone is used some improvement occurs in the pathological state of the cerebrospinal fluid in fully 60% of cases. This improvement is not sufficient to guarantee permanent benefit (confirmed by my own experiences); also, it has to be remembered that similar improvement in the cerebrospinal fluid in cases of general paresis may result from initial treatment with arsenical preparations, only to be followed by relapse at a later stage. So far as I am aware no case of general paresis has been reported to have become serologically negative in both cerebrospinal fluid and blood, with the maintenance of clinical improvement, on penicillin treatment alone. The best results appear to have been obtained in those cases treated with penicillin in combination with some form of pyrexial therapy (Goldman, 1945). Some clinicians have used a total dosage of 3,000,000 units of penicillin in conjunction with only "half the usual amount of fever therapy." Rose and his co-workers (1946), for instance, report 49 cases of general paresis receiving this form of treatment: 25 improved, 21 showed no change, and 3 became worse.

In cases of general paresis treated with full malarial or fever therapy, whether or not followed by courses of arsenical and bismuth injections, the positive serological reactions in blood and cerebrospinal fluid take two to four years to become negative. The addition of an initial course of penicillin to therapeutic malaria certainly appears to hasten the reversal of the positive serological reactions, especially in the cerebrospinal fluid.

From my personal experiences the scheme I would advocate for the treatment of general paresis is as follows:

After four initial injections of bismuth—for example, bismostab 0.5 ml., or metallic bismuth 0.2 g.—to obviate Herxheimer-Jarisch reactions, a full course of intramuscular penicillin is given in doses of 40,000 units every three hours (preferably), or 300,000 units every 12 hours, for a total dosage of 4,000,000 or even 5,000,000 units. This is then followed by the usual standard course of fever therapy—e.g., induced malaria to 12 rigors if possible, or at least 10. Arsenic and bismuth therapy is then given in weekly doses of neoarsphenamine (0.45 g.) or mapharsen (0.06 g.) or "acetylarsan" (diethylamine acetarsone) (3 ml.) and bismuth—e.g., 1 to 0.5 ml. of bismostab=20% suspension of precipitated metallic bismuth in isotonic glucose solution. Twelve injections of each substance constitute a course. Three such courses should be attempted during the year, the intervals between them depending upon the patient's tolerance and progress. The cerebrospinal fluid is examined every six months and treatment is continued until the serological reactions become negative. A further examination should be made six months later and then at intervals of one year for two years.

In cases of general paresis in which malarial or fever therapy is contraindicated by reason of hyperpiesis or cardiovascular disease one needs to rely on penicillin alone. So far I have had only two such cases, which I have been able to follow up for an appreciable period.

One case, that of a woman aged 47 with early general paresis showing the usual and typical cerebrospinal fluid changes (14 small lymphocytes, total protein 60 mg., Lange curve of paretic type, strongly positive Wassermann reaction, and Meinicke 4431), had aortic valvular disease with regurgitation and a blood pressure of 250/100. She was given 10,000 units of penicillin intrathecally in 10 ml. of saline daily for nine days, and at the same time the standard course of 40,000 units of penicillin every three hours for 7½ days, by parenteral injection. No noteworthy therapeutic reaction occurred, and meningeal reaction following the first intrathecal injection was comparatively slight (cerebrospinal fluid 420 cells—60% polymorphs and 40% lymphocytes—and total protein 100 mg.). Two months later the cerebrospinal fluid showed only two cells, total protein 25 mg., Wassermann reaction negative, and Lange curve still paretic. The blood Wassermann reaction was still strongly positive. Six months later her clinical condition remained satisfactory and the cells and total protein of the cerebrospinal fluid were normal; the Wassermann reaction of the cerebrospinal fluid, however, was now weakly positive and that of the blood still strongly positive.

The second case was that of a man aged 45 with early general paresis, hyperpiesis—blood pressure 240/120—and enlarged left ventricle. The cerebrospinal fluid changes were typical, with strongly positive Wassermann reaction and paretic Lange curve. The usual standard course of penicillin by intramuscular injection was given. He received no intrathecal treatment. Three months after treatment the cell and total protein content in the cerebrospinal fluid were normal and the Wassermann reaction was negative; the Lange curve was still paretic and the blood Wassermann reaction positive. Six months later (nine months after penicillin treatment) his clinical condition had remained more or less stationary, but the cerebrospinal fluid Wassermann reaction was positive, as was that of the blood; the Lange curve was still paretic in type.

The persistence of the paretic Lange curve in both cases is of interest. With the tendency to serological relapse in these cases, it would seem inadvisable to rely on penicillin alone in the treatment of general paresis if malarial or fever therapy is likely to be tolerated. To detect any tendency to relapse the cerebrospinal fluid should be examined at intervals of six months until the serological reactions have been negative for two years, clinical improvement having been maintained. Taboparesis is treated in the same manner as general paresis.

(b) Tabes Dorsalis

No dramatic change is to be expected in tabes dorsalis following penicillin treatment, although in common with other forms of neurosyphilis a pathological cerebrospinal fluid usually shows definite improvement, and there is an

improvement in symptoms—even if temporary—in some 40% of cases.

As a result of earlier experiences I have not been in favour of treating tabes dorsalis with malarial or fever therapy; this I have stated elsewhere (Worster-Drought, 1940). After two or three years' intensive treatment with courses of arsenical and bismuth therapy most cases of tabes dorsalis (and especially early cases) can be arrested and the serological reactions rendered negative. Admittedly, a negative serology does not necessarily indicate arrest of the disease process, and some symptoms—more particularly attacks of lightning pains—are apt to persist.

I now treat cases of tabes dorsalis with an initial course of penicillin given intramuscularly. Although all the earlier cases received the usual standard course I have treated later cases with a larger total dosage (40,000 units every three hours, up to a total of 4,000,000 or 5,000,000 units); other cases have received larger doses at longer intervals (300,000 units every 12 hours or 500,000 units every 24 hours, for eight days). The course of penicillin is then followed up with arsenical (neoarsphenamine or acetylarsan) and bismuth therapy in the usual doses. I intend to continue this arsenical–bismuth treatment up to one or two years, according to the progress of the patient's symptomatology and serological reactions, which are determined from time to time at the same intervals as given for general paresis.

Attacks of so-called lightning pains often persist in tabes dorsalis even when other symptoms are absent and when the disease is apparently arrested, or at least has reached a quiescent stage, and long after the serological reactions have become negative and the cerebrospinal fluid is normal. I have now treated several cases showing negative serological reactions with courses of penicillin by intrathecal and intramuscular injection combined and by intramuscular injection alone. The results as regards the lightning pains have been variable. In a few cases treated by intramuscular injections only (the usual standard course), relief from lightning pains has occurred without relapse over periods of observation up to 12 months. In other cases a remission of several months' freedom from these pains has followed the course of treatment—that is, considerably longer intervals between the attacks of pain than before treatment—while other cases have remained unaffected.

I have also treated a few cases (tabes dorsalis with negative serology and apparent quiescence of the disease apart from the lightning pains) with penicillin given intrathecally (10,000 units in 10 ml. of saline daily for eight days and accompanied by the usual standard course of penicillin injections intramuscularly), and the results as regards subsequent freedom from lightning pains (up to six months' follow-up observation) have been rather better than in those cases treated by parenteral injection alone. The disadvantage of intrathecal treatment, apart from the usual risks, in these cases, however, is that the first intrathecal injection of penicillin is apt to provoke a very severe attack of generalized nerve-root pain accompanied by pyrexia and considerable meningeal reaction.

Some cases of gastric crises have been definitely improved by penicillin treatment, but a few have remained unaffected. I have not observed any material change in Charcot's arthropathy as a result of penicillin treatment.

(c) Primary Optic Atrophy

I have been able to convince myself that malarial therapy (preferably followed by bismuth and arsenical treatment) is capable of arresting primary optic atrophy of syphilitic origin (tabes optica) from a series of cases followed up to six years after treatment. It is known that 75% of untreated cases become totally blind within three years and 100% within five years (Lehrfeld and Gross, 1938). Consequently the observation of any patient treated must extend to five years or longer before success can be claimed.

The experiences of Moore, Woods, Hopkins, and Sloan in America, ranging from 1932 to 1942, also confirm the beneficial effects of malarial therapy in primary optic atrophy. Only 14.6% of 16 cases of primary syphilitic optic atrophy became blind within three years of treatment, and thereafter there was no rise in the incidence of blindness.

"Excellent initial effects" following penicillin treatment are reported by some observers. Rose and his co-workers (1946) record "apparent arrest of visual loss" in five of six cases of primary optic atrophy treated with penicillin and half the usual amount of fever therapy. In view of the fact, mentioned above, that primary optic atrophy can slowly progress for five years before blindness ensues, it is clearly far too early to consider possible arrest of primary optic atrophy following penicillin treatment alone, and I doubt if complete arrest is possible as a result of penicillin treatment, however administered, without concomitant fever therapy.

I would still advocate full malarial or fever therapy in primary optic atrophy, but I now start treatment with a course of intramuscular penicillin (total dosage of 4,000,000 units) and follow this with 10 to 12 malarial rigors, according to the patient's tolerance. Also, I prefer to follow the malaria with arsenical and bismuth therapy until the serological reactions become negative.

(d) Late Asymptomatic Neurosyphilis

Asymptomatic neurosyphilis is a term applied to the condition in which pathological changes due to syphilitic infection exist in the cerebrospinal fluid but the patient neither complains of symptoms nor shows any abnormal neurological signs.

Two types of asymptomatic neurosyphilis must be distinguished: (1) That occurring in the earlier stage of syphilitic infection coincident with or shortly after the secondary stage or period of general invasion (early asymptomatic neurosyphilis). This form of the disorder is of meningovascular type and readily amenable to treatment. (2) That detected long after primary infection as a result of an examination of the cerebrospinal fluid either because the blood has been found to yield a positive Wassermann reaction—for example, in a proposed blood donor—or during the routine investigation of a patient with a history of syphilis (late asymptomatic neurosyphilis). It is probable that this latter type is classifiable as a form of parenchymatous neurosyphilis in that the pathological changes in the cerebrospinal fluid are only slightly, if at all, influenced by intensive treatment with the ordinary antisyphilitic remedies. Observations have shown that late asymptomatic neurosyphilis often terminates in general paresis—a fact that led Solomon to term the condition "paresis sine paresi." Even with malarial or fever therapy followed by arsenical–bismuth treatment three or four years may elapse before the serological reactions in the blood and cerebrospinal fluid are favourably influenced.

From the reports on penicillin treatment applied to asymptomatic neurosyphilis it is clear that not sufficient distinction has been drawn between the "early" and the "late" type. As a form of meningovascular neurosyphilis early asymptomatic neurosyphilis is rapidly and favourably influenced by penicillin. Also, so far as can be judged at so early a stage, penicillin is most valuable in the treatment of late asymptomatic neurosyphilis even if regarded only as an additional measure. Reports indicate improvement in the cerebrospinal fluid of many cases treated with penicillin alone, although in some of the records it is by no means clear whether the authors are including cases of early asymptomatic neurosyphilis. Stokes and his co-workers (1946) report improvement in 60% of cases of asymptomatic neurosyphilis; also Lloyd-Jones and his co-workers (1946) report that of 10 cases treated with massive daily doses of penicillin (300,000 to 500,000 units) given intramuscularly to a total dosage of 2,400,000 to 5,000,000 units, the cerebrospinal fluids of four of the 10 cases reverted to normal within six weeks (these cases may have been examples of early asymptomatic neurosyphilis). Although the cerebrospinal fluids of the remaining six cases showed improvement (as one would expect) they had not become serologically negative at the time of reporting.

Owing to the known severity of late asymptomatic neurosyphilis as regards prognosis, my view is that the condition should be treated with a full course of penicillin consisting of a total dosage of at least 4,000,000 units given by intramuscular injection in doses of 40,000 units every three hours (preferably), of 300,000 units every 12 hours, or of 500,000 units every 24 hours; with the last-mentioned method the total dosage should

be 5,000,000 units. The period of penicillin therapy is then followed by full pyrexial therapy—for example, malaria, 10 to 12 rigors—and, finally, by the usual arsenical–bismuth therapy until the cerebrospinal fluid is normal and the serological reactions are negative. As with other cases of neurosyphilis, the cerebrospinal fluid should be examined at intervals of six months, and, following a negative result, at yearly intervals for two years.

(e) Erb's Syphilitic Spinal Paralysis

This form of parenchymatous neurosyphilis (antero-lateral spinal sclerosis of syphilitic origin) results from degeneration in the antero-lateral portions of the spinal cord, and is notoriously resistant to treatment by all previously known methods. Tucker (1946) has treated four cases with penicillin, giving a total dosage of 2,000,000 to 10,000,000 units by intramuscular injection in repeated doses of 25,000 units every three hours for 10 to 25 days. No improvement resulted. One patient died, six months after treatment, from *Clostridium welchii* infection, and the other three failed to show improvement after 121, 376, and 582 days. In the only case I have been able to treat with penicillin the result was similar.

Summary and Conclusions

Penicillin has a definite and established place in the treatment of neurosyphilis.

Most of the present-day experiences are based on the "standard" course of penicillin established in 1944 for the treatment of early syphilis in the British Services and in the U.S. Army in Europe (a total dosage of 2,400,000 international units given by parenteral injection in doses of 40,000 units every three hours, day and night, for seven and a half days).

In view of the percentage of relapses even in early syphilis it is considered doubtful if this course is sufficient for neurosyphilis. It is suggested that a total dosage of at least 3,000,000 units be given to all cases of neurosyphilis and that in parenchymatous neurosyphilis the total dosage should reach 4,000,000 to 5,000,000 units.

It may prove unnecessary to keep penicillin in the blood at as high a continuous level as possible throughout the period of treatment. If so, equally good therapeutic effects may be obtainable with larger doses of penicillin given at longer intervals (300,000 units given every 12 hours or 500,000 units every 24 hours for 8 to 15 days). Such a method would enable cases of chronic neurosyphilis to be treated as out-patients.

Intramuscular injection is the best method of administering penicillin. For reasons given, the intravenous route—either by continuous drip or by repeated single injections—has little to commend it.

There is no evidence that the intrathecal administration of penicillin is of greater therapeutic value in neurosyphilis than when the remedy is given by intramuscular injection. Because of the resulting reactions and the various additional risks intrathecal injection of penicillin is best avoided in most cases of neurosyphilis.

Owing to the risk of possible Herxheimer-Jarisch reactions following the first doses of penicillin, all cases of neurosyphilis should receive an initial series of bismuth injections before starting the full course of penicillin.

The rapid beneficial effects of penicillin on the cell and protein content of the cerebrospinal fluid suggest a special selective action on the meninges or cerebrospinal fluid.

In meningovascular neurosyphilis the course of penicillin should be followed by full arsenical and bismuth therapy in view of the percentage of relapses, even in cases of early syphilis treated with penicillin alone.

General paresis is best treated with an initial course of penicillin of total dosage of 4,000,000 to 5,000,000 units followed by full malarial or fever therapy (10 to 12 malarial rigors). Finally, the usual courses of arsenic and bismuth are advisable until the serological reactions become negative.

In cases of general paresis (and taboparesis) in which malarial or fever therapy is contraindicated by reason of cardiovascular disease, one must rely on penicillin alone. Some improvement, but not cure, can be expected.

In tabes dorsalis no dramatic change follows penicillin treatment. Cases are best treated with an initial course of penicillin and then with the usual courses of arsenicals and bismuth for two to four years until apparently quiescent and the serological reactions have become negative. Special symptoms such as lightning pains and gastric crises benefit from penicillin in some cases, including those in which the serological reactions are already negative.

Primary optic atrophy of syphilitic origin can be arrested in a fair proportion of cases by malarial therapy. Penicillin alone is not likely to arrest the optic atrophy, but may prove useful in hastening arrest or in bringing about arrest in an even larger proportion of cases. Treatment should consist of an initial course of penicillin of total dosage 4,000,000 to 5,000,000 units, followed by full malarial therapy (10 to 12 rigors) and afterwards arsenicals and bismuth. Observation of any patient must extend to five years or longer before success can be claimed for any form of treatment.

A distinction must be drawn between early asymptomatic neurosyphilis and late asymptomatic neurosyphilis. The latter condition, being of serious import, must be treated with penicillin and malarial or fever therapy on the same lines as general paresis.

At least five years must elapse before we can determine fully the value of penicillin in neurosyphilis.

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