THE TREATMENT OF PRIMARY AND SECONDARY SYPHILIS

By R. R. WILLCOX, M.D.
St. Mary's Hospital, London, W.2

A dozen years have now elapsed since Mahoney and his colleagues (1943) first reported the use of penicillin for the treatment of early syphilis. Since that time there has been a gradual but consistent extension of its use as the sole agent for the treatment of this disease. Indeed, in a World Health Organization survey of 277 leading venereal clinics in 55 countries of the world made in 1953 and reported by Willcox (1954), no less than 94.2 per cent. of clinics used penicillin for the treatment of early syphilis and 65.3 per cent. without other drugs. It was noted that Europe lagged behind the other countries of the world in its adoption of penicillin as the sole curative agent.

During these years, also, there has in developed countries been a dramatic fall in the prevalence of venereal syphilis. Currently the number of new cases of early syphilis treated annually in the clinics of England and Wales is about one-twentieth of what it was in the peak year of 1946, and less than one-sixth than before the war. It is, therefore, timely to consider what is the optimal treatment of early syphilis today. To do this adequately it is necessary to commence the story with the four cases treated by Mahoney and his colleagues in 1943.

Amorphous Penicillin

In three cases Mahoney *et al.* used 25,000 units of aqueous amorphous penicillin given every four hours for 48 injections. (Total 1.2 mega units.) It has been shown that the *minimum* duration of penicillinaemia required to cure syphilis experimentally in rabbits is 96 hours. The height of the serum level of penicillin is of relatively small significance, since, generally speaking, a detectable serum level (0.03 unit per ml., or above) for a sufficient time is all that is required to cure syphilis. It is the duration of the penicillinaemia which is all-important and considerations of dose only apply to their effect upon the duration of penicillinaemia.

In 1943 the Allied armed forces were finding the long-term continuous treatments for syphilis with arsenic and bismuth, and entailing weekly attendances at hospital on and off for a year, were an appreciable strain on their already extended manpower. Indeed, attempts were being made to intensify schedules using arsenoxide, sometimes with fatal toxic results. The opportunity of obtaining a rapid and, above all, safe treatment for syphilis was more than welcome. The U.S. authorities doubled the dose used by Mahoney and 2.4 mega units of amorphous penicillin given over seven and a half days (usually in 60 three-hourly injections) became a schedule which enjoyed world-wide general use.

Crystalline Penicillin G (Benzyl Penicillin)

The early penicillins were brown powders of a low unitage per milligramme and containing an appreciable quantity of impurities. As data as to the effects of penicillin upon early syphilis accumulated failure rates of 15 per cent. at one year and 25 to 35 per cent. at two years were noted (Moore, 1949). Failure rates are higher in cases of secondary syphilis than in primary syphilis, and therefore when failure rates with different schedules are compared only secondary cases should be considered. However, at this time failure rates were, paradoxically, not always related either to dosage or to treatment time.

This led to the discovery of penicillin fractions, G, F, X and K. Penicillin G was then shown to be many times more effective than the K fraction, which, in the striving for greater purity, expressed in unitage per milligramme, was being unconsciously included more and more in many commercial amorphous penicillins. Crystalline penicillin G (benzyl penicillin) was soon isolated and has been the routine basic penicillin for the treatment of syphilis for the last eight years. As penicillin became more plentiful the dose given for early syphilis rose to 4.8 mega units over seven and a half days, but with benzyl penicillin injections still had to be given every few hours to maintain the penicillinaemia.

Penicillin in Oil-Beeswax

As might have been expected, efforts were soon directed towards the prolongation of penicillinaemia following a single dose. Two approaches were made: (a) by delaying absorption and (b) by delaying excretion. Although success was ultimately obtained with caronamide and other substances in delaying excretion, the delayed absorption methods had by this time already become established as being both effective and safe.

The first successful repository preparation was penicillin in oil-beeswax evolved in 1945 by Romansky and Rittman. This preparation contained 300,000 units of calcium penicillin per ml. of arachis oil, with 4.8 per cent. of beeswax. Single intramuscular injections of 1 ml. of this would provide a penicillinaemia long enough to cure gonorrhoea. Following a 2-ml. dose (600,000 units), appreciable serum levels could be maintained for 24 hours or more. The out-patient treatment of both gonorrhoea and syphilis with penicillin was then possible. For early syphilis eight daily injections of 600,000 units of penicillin in oil-beeswax became a standard method of penicillin administration.

Even with these developments some treatment failures were still reported, although a number of observers insisted that many of the so-called failures were, in fact, reinfections, it being possible to be reinfected with syphilis as soon as penicillinaemia has ceased. Subsequent events have largely supported this view, for certainly as the prevalence of syphilis has declined, more so have the numbers of reported ' failures.'

Procaine Penicillin

More recently it was discovered that the monohydrate salt of procaine would combine in equimolecular amounts with benzyl penicillin to produce a sparingly soluble salt which can be suspended in water (with the addition of carboxymethyl cellulose) to form a stable suspension, or in oil. With these preparations serum levels can be made to run consistently well beyond 24 hours and, moreover, aqueous procaine penicillin will pass without difficulty through a 20-gauge needle.

Aqueous procaine penicillin G replaced penicillin in oil-beeswax in British and other pharmacopoeias and eight daily injections of 600,000 units came to be an acceptable method of giving penicillin in the treatment of early syphilis.

Procaine Penicillin G with Aluminium Monostearate (PAM)

From procaine penicillin came procaine penicillin with aluminium monostearate (PAM) developed by Buchwalter and Dickinson in 1948. By using a suspension of procaine penicillin G in oil gelled with 2 per cent. aluminium monostearate it was shown that detectable levels of penicillin could be obtained for 72 hours or more after 300,000 units (1 ml.). Increasing the dose does not proportionately increase the duration of the effective level, although after 2.4 mega units a penicillinaemia may be maintained for eight days or more.

This new development at once indicated that it should be theoretically possible to cure syphilis with but a single injection. Thomas *et al.* (1953) have reported on such single-injection techniques and the failure rates of 12 to 15 per cent. obtained were considered to be in line with those experienced with previously tried methods. Such techniques had immediate application in the mass treatment campaigns against the treponematoses organized by the World Health Organization, for in mass treatment it is well worth while, if necessary, to lose a little therapeutic efficiency for the sake of simplicity. At the same time, those accustomed to daily injection schedules continued to use them and eight daily injections of 600,000 units of PAM came to replace those of aqueous procaine penicillin and penicillin in oil-beeswax.

Unfortunately, not all preparations of PAM (including a number of British) were able to achieve the penicillinaemia of which the preparation is capable. This was due in the main to the penicillin particles being too large. While not important when daily injection schedules are used (as adequate coverage from injection to injection was, even before PAM, more than sufficient), for the treatment of the treponematoses in the underdeveloped areas a sufficient duration of penicillinaemia is most necessary.

The World Health Organization therefore formulated a number of specifications for PAM preparations to be used in their mass campaigns (Guthe *et al.*, 1953). The most important of these is that, following a single intramuscular injection of 1 ml. (300,000 units), a serum level of 0.03 unit per ml., or above, should be maintained for 24 hours or more in the majority of subjects. These specifications have done much to raise the standards of PAM generally.

During 1952 the World Health Organization Expert Committee on Venereal Infections and Treponematoses met in London (WHO, 1953) and suggested a number of possible acceptable schedules for the treatment of early syphilis with PAM. For primarily syphilis a minimum of 2.4 mega units was recommended and of 4.8 mega units for secondary syphilis. It is personally felt that all cases of early syphilis (in countries where there is no shortage of penicillin) should receive the dosage recommended for secondary syphilis and these are therefore given in the table.

TABLE 1.—WORLD HEALTH ORGANIZATION SUGGESTED DOSAGE OF PAM FOR TREATMENT OF SECONDARY SYPHILIS (MEGA UNITS OF PAM TO BE GIVEN ON THE FOLLOWING DAYS).

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
4.8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2.4	—	—	—	2.4	—	—	—	—	—	—	—	—	—	—	—	—
2.4	1.2	1.2	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2.4	—	1.2	—	1.2	—	—	—	—	—	—	—	—	—	—	—	—
2.4	—	—	1.2	—	—	1.2	—	—	—	—	—	—	—	—	—	—
2.4	—	—	—	1.2	—	—	—	1.2	—	—	—	—	—	—	—	—
2.4	0.6	0.6	0.6	0.6	—	—	—	—	—	—	—	—	—	—	—	—
2.4	—	0.6	—	0.6	—	0.6	—	0.6	—	—	—	—	—	—	—	—
2.4	—	—	0.6	—	—	0.6	—	—	0.6	—	—	0.6	—	—	—	—
2.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	—	—	—	—	—	—	—	—
2.4	—	0.3	—	0.3	—	0.3	—	0.3	—	0.3	—	0.3	—	0.3	—	0.3

These schedules indicate the considerable latitude which is possible using PAM. Other schedules based on the above, and more extravagant in penicillin, are, of course, devised.

All of the schedules recommended by the World Health Organization, however, have one thing in common—namely, the initial dose of 2.4 mega units, which has by itself been shown to be curative in most cases of early syphilis. Thus a minimal curative dose is given at once, so, should the patient default and not obtain the remainder of the treatment, no harm will result. This so-called 'epidemiological dose' has everything to recommend it.

Position in this Country

When penicillin was first introduced for the treatment of syphilis the traditional conservatism of British clinicians rendered them loath to accept the new concepts of treatment at their face valuee As a result they retained, in addition to the intensive curative penicillin course, a sub-curativ. 'consolidation' course of 10 weekly injections of arsenic and bismuth. As toxic reactions from the arsenic (dermatitis, agranulocytosis, etc.), which were sometimes severe and occasionally fatal, still occurred, the arsenic was dropped, but the bismuth was retained for longer; indeed, not all clinics have yet abandoned it. As the arsenic and bismuth was gradually forsaken, it tended to be replaced with weekly or bi-weekly injections of PAM, it being believed that there is nothing which arsenic and bismuth can do which penicillin cannot achieve more effectively and more safely.

Today consolidation treatment is practised most in Europe; indeed, by 59.1 per cent. of European clinics, as compared with no North American clinics in the WHO survey (Willcox, 1954). Of the European clinics as a whole, about one-quarter used penicillin for consolidation, but for the British Isles the figure was 40 per cent.

However, early syphilis being scarce and supplies of penicillin abundant, there is no harm in giving six to 10 bi-weekly or weekly injections of 900,000 to 1,200,000 mega units of PAM in addition to the initial intensive course. Indeed, in these circumstances, if an initial dose of 2.4 mega units is given, the intensive course may be omitted altogether. This is a great advantage in small clinics and in private practice.

Newer Developments: Benethamine and Benzathine Penicillins

Since PAM have come benethamine and benzathine penicillins. *Benethamine penicillin* (N-benzyl-β-phenylethylamine salt of penicillin G) as an aqueous suspension is easier to handle than the oily PAM and will procure blood levels of a similar or longer duration. The injection is somewhat painful and for this reason aqueous suspensions of benethamine penicillin have not superseded PAM. This difficulty can be overcome by using an oily suspension and trials with this are currently under way in the World Health Organization mass campaigns.

Benzathine penicillin (N,N': dibenzylethylenediamine dipenicillin G, commonly known as DBED penicillin), developed by Szabo *et al.* (1951), on the other hand, promises to open up new horizons in syphilotherapy. Following a dose of 2.5 mega units of benzathine penicillin detectable serum levels of penicillin may be maintained for 16 days or more, and some observers have found detectable levels after a month in some cases. In American trials using single injections of 2.4 to 2.5 mega units of this penicillin results have been in every way comparable (retreatment rates of 6 per cent. at one year) with those obtained with 4.8 mega units of PAM given by multiple injections (Shafe and Smith, 1954; Smith *et al.*, 1954). Other experience (e.g. Vilanova and Alvarado, 1954) confirms this view.

The utilization of benzathine penicillin for syphilotherapy has been retarded by the painful local reactions and occasional febrile reactions encountered with some preparations. Not all of

the world's benzathine penicillins cause pain and it is anticipated, therefore, that this obstacle will be successfully overcome. When this has been achieved it will be quite pointless any longer to persist with daily injections of penicillin. Treatment will consist of an epidemiological dose of 2.4 mega units of benzathine penicillin followed by nil to four weekly injections of 1.2 to 2.4 mega units of the same preparation. Until then it is likely that PAM will continue to be used in the manner described. So-called ' all-purpose ' penicillins are not considered in this paper. They are only a mixture of those described.

Side-effects of Penicillin

On the whole, there have been few side-effects, certainly far less than were experienced in the days of metal chemotherapy. Urticaria (usually controlled by antihistamines) and dermatitis are the commonest, although in recent years there have been a small but increasing number of anaphylactic type of reaction, some of which have been fatal. This increase is doubtless linked to the increasing proportion of the population who have at some time received the drug. An alternative to penicillin should seriously be considered in all cases in which there is a history of penicillin sensitivity in the past.

Lest the importance of these reactions should be exaggerated, Shafer (1954) reported that in the years 1946-50 some 185,577 patients were treated with penicillin in 36 American V.D. clinics. There were only 578 reactions (3.11 per 1,000), including two deaths. Of 70,037 patients treated during 1950-52, only 56 (0.8 per 1,000) had severe reactions with no deaths.

Other Antibiotics

Penicillin, chloramphenicol, the tetracycline antibiotics (tetracycline, chlortetracycline and oxytetracycline), erythromycin and, it is said, spiramycin are all active against *T. pallidum*, streptomycin far less so. Penicillin has been shown to be the most effective experimentally and penicillin by injection gives better and more sure results than any orally-administered preparation. The other antibiotics may be reserved for persons showing sensitivity to penicillin.

Follow-up of Treated Case

Although the treatment of syphilis has been markedly reduced as the result of penicillin, it is not possible to curtail the period of post-treatment observation to the same degree.

The generally accepted regime is for the patient to have a clinical and serological examination once a month for six months, every quarter for a year and every six months for a second year, during which time an examination of the spinal fluid is made.

Although reinfection (possibly from the same partner) may occur at any time, clinical and/or serological relapse is most to be expected within six or nine months from treatment. It is necessary that one of the serum tests used be quantitated so that any changes in titre may be observed. Retreatment because of sero-resistance, providing the titre is not increasing, is not necessary before six to 12 months after treatment has elapsed. If the titre is declining, one can afford to continue to watch it do so.

In large numbers of treated persons followed up for some years no appreciable incidence of neurosyphilis or of cardiovascular syphilis have been found in those who have successfully passed the tests of cure indicated.

Management of Contacts

All sexual contacts of the patient should be examined. If these are clinically and serologically examined once a month for three months from the last risk of infection and the tests are negative, they may be considered to be free.

A controversial point is whether asymptomatic contacts should be treated in the absence of clinical or serological evidence of the disease. Regular consorts are at a high risk of contracting syphilis and, should they do so, if they have not been secured for examination, might reinfect the original patient (' ping pong ' syphilis). If treated, on the other hand, they are unlikely to contract the disease. Contacts treated in this way should, however, be given the full post-treatment surveillance (including lumbar puncture at two years) just as if the disease had been known to be present. This fact removes the usefulness of the procedure, as without such treatment the disease would declare itself within three months and many contacts would suffer no further inconvenience and feel no stigma that they had had syphilis. In many parts of the world, however, the majority of asymptomatic contacts will not or cannot attend for surveillance for the necessary three months and for these persons—in whom considerations of follow-up no longer apply—the procedure is justified (Willcox, 1954). Similarly, as a control measure in areas where syphilis prevalence is high, the regular use (say once a month) of the long-acting benzathine penicillin has been considered in prostitutes (Guthe, 1955). There does not seem to be any danger of penicillin resistance of the treponeme, but there may be from penicillin sensitivity of the host.

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Continued on page 557

OTHER WHEAT STARCH RECIPES

Wheat Starch Cake

½ lb. wheat starch
4 oz. sugar
4 oz. margarine
1 teaspoonful salt
3 teaspoonsful baking powder
4 oz. milk
1 egg (optional)
Flavour with coconut, dates or chocolate

Method: Sieve the dry ingredients into a basin, run in the margarine, then make a well in the centre and mix enough to make a soft dough. Mix quickly and lightly and turn the dough into a well-greased shallow tin. Bake about 30 minutes in a hot oven (400° F.) or regulo 7.

Biscuits

8 oz. wheat starch
4 oz. margarine
4 oz. castor sugar
1 egg (small)
Grated orange rind or vanilla

Method: Cream margarine and sugar, add the egg and then the flour. Knead lightly to a small ball. Roll out thinly, prick all over and cut into shapes. Place on a greased tin. Bake in a moderate oven for 15 minutes. Regulo 4 or 250° F.

This mixture will make 1 lb. biscuits.

These biscuits can be made without sugar and may be used with butter or jam, etc.

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