DISCUSSION ON THE PENICILLIN TREATMENT OF SYPHILIS

LIEUT.-COL. J. W. EAMES thought that the results of a survey of cases treated with penicillin in recent years might be of interest. In 1944, 2-4 mega units of penicillin were given in the Army in the treatment of early syphilis, and a preliminary survey of case records after six months revealed a failure rate of 8 per cent. Since then, further methods of treatment had been used, and he would mention some of the results, which were part of a report in course of publication. Owing to the release and posting of personnel, follow-up of Service cases was far from being easy. For example, the loss by release from the Service in one particular group was such that, of 395 cases, only 288 were left after six months and 125 after one year. In order to offset these losses, Prof. Lancelot Hogben had arrived at an actuarial formula by which failure rates were calculated. In the cases of patients suffering from primary syphilis treated with 2-4 mega units of penicillin (aqueous solution) over a period of seven and a half days, the maximum incidence of relapse occurred in the first six months, and by using this formula it was found that at twelve months the cumulative relapse rate, in round figures, for sero-negative primary cases was 14 per cent., for sero-positive primary 13 per cent., and for secondary cases 17-5 per cent. In patients treated by means of 4 mega units of penicillin in twelve and a half days the relapse rate, as far as could be seen from the small follow-up, appeared to be essentially the same.

The results of treatment consisting of 2-4 mega units of penicillin plus 0-6 g. mapharside in ten days, and a similar course giving 0-4 g. mapharside and 1 g. of bismuth did not appear to differ materially from those in which penicillin alone was used. However, owing to release from the Army, the number followed up was comparatively small. It must be remembered that during the period under survey release was at its height.

As regards sero-resistance (failure of any tendency to sero-reversal in four months), in sero-positive primary cases treated by 2-4 mega units resistance occurred in 3 per cent. of cases, and in secondary cases in 8 per cent. When 4 mega units of penicillin were given, sero-positive primary cases showed a resistance rate of 1-6 per cent., and secondary cases 3-8 per cent.

Present treatment in the Army consisted of 50,000 units of penicillin three-hourly for a period of ten days, combined with 1-35 g. N.A.B. and 0-3 g. bismuth in divided doses on the second, fifth, and ninth days, followed by 0-6 g. N.A.B. and 0-2 g. bismuth weekly for eight weeks, but it was too early yet to evaluate this scheme.

It had been suggested that bismuth, being a heavy metal, might have an adverse effect on the penicillin content of the blood. A small series of cases was investigated, and the results, allowing for experimental error, did not differ from those cases treated with penicillin without bismuth.

MR. A. J. KING said he had not been convinced by various reports of a high incidence of failure in cases of early syphilis treated with penicillin alone. These reports were based on small numbers, in which an exceptionally bad run was always possible, and such findings did not accord with his own experience. Now that Dr. Moore had produced the figures the evidence was clear enough, and it was time for opinions to be revised. He felt that important evidence on this point was also to be found in this country by those who took the trouble to collect it. Many patients with early syphilis had been treated in the Services with penicillin alone, and a number of them were under observation at the various public clinics. Dr. Curtis and he had gone into the subject of patients who had attended the Whitechapel Clinic for follow-up since leaving the Services. They had limited the enquiry to those who had received 2-4 mega units of penicillin by the method of sixty three-hourly injections of 40,000 units each in watery solution. Eighty-two patients had been found who had been under observation for at least a year, and many of them for two years or more, and the treatment had failed in only four cases. This was a very small group and obviously was not for comparison with the figure Dr. Moore had cited. He put it forward in the hope that medical officers at other clinics would make similar investigations, so that ultimately there would be a large number of cases observed for a long period.

DR. FORGAN noted that Dr. Moore had compared results with penicillin in oil beeswax suspension in a total of 4-8 mega units with the results obtained with 2-4 mega units of aqueous solution of penicillin, and he wished to ask if the aqueous solution had been given in the higher dosage.

Some of the American reports were exclusively on white male adults, and he wondered if workers in America had found any evidence to support the theory that the optimum amount of penicillin for negroes might be less than for whites. It had been claimed in South Africa that smaller amounts of arsenic and bismuth were required.

He wondered whether American syphilologists resembled their British colleagues in declaring that if they themselves had the misfortune to contract syphilis they would not be content to rely on penicillin. Were the latest results of crystalline penicillin G so good that an infected American doctor would dare to dispense altogether with metallotherapy?

DR. DAVID NABARRO said that there was one particular phase of Dr. Earle Moore's work to which he would draw attention and that was the extraordinarily interesting results which had been obtained in the antenatal treatment of the expectant mother. It was remarkable that this treatment was not adopted in this country. Only last
week he saw a mother who had attended an antenatal clinic; her blood was found positive and nothing was done. The child was brought to Great Ormond Street and died of congenital syphilis. Such a thing should not happen today. When such a drug as penicillin was available it was criminal that infected pregnant mothers should not be treated.

Dr. Moore's figures reminded them of what happened in the early days of salvarsan, when it was hoped that one injection of 606 would cure the patient, and it seemed that the same tale would be unfolded in the treatment of syphilis with penicillin. There was another point: could penicillin modify the disease so that the patient appeared to be cured and yet in the course of time the spirochete was able to infect any children who might be born. He came across several cases during the war of soldiers with congenital syphilis which had never been recognized. The training which they had undergone seemed to be too much for them. Several of them were thought to be cases of encephalitis, whereas investigation of the spinal fluid showed that they were cases of congenital paraxis. It might appear that the disease was cured, but later on a mother might give birth to children with modified congenital syphilis which it would be difficult to recognize.

He wished to impress upon the medical fraternity the point that every expectant mother should have a blood test, and that if she was found positive she should be treated. She need not be treated with a toxic drug.

Why congenital syphilitic children responded more readily to penicillin than adults he could not say. It was a very interesting point but there was no doubt that children were still dying from congenital syphilis in this country.

Dr. Joseph Earle Moore, in reply to the discussion, said, with reference to Dr. Lourie's series, that one of the things which had been learned and of which he was firmly convinced, was that little or nothing could be said about the results of a small series of patients from any individual clinic. Working with some thirty-five to forty different clinics he had found that clinics using identical treatment schemes had turned up with widely variable results. One clinic in the United States had taken the point of view that the administration of penicillin every two hours, instead of every three, decreased the failure rate almost to the vanishing point. This clinic had treated 800 patients with 3.4 million units of penicillin administered every two hours day and night for an eight-day period, with a failure rate of only about 2 per cent. Three other clinics using 4.8 million units every two hours day and night for an eight-day period, an identical treatment system for the same period, except for more penicillin, had failure rates comparable with those of other systems, that is, 25 to 30 per cent. When a clinic turned up with a cumulative failure rate of only 1 or 2 per cent., the validity of the observation seemed questionable.

In reply to the question "What would you do if you got syphilis?" he would give details of the treatment he gave in his private practice. In his country patients who could afford to pay for hospitalization could not obtain it on short notice. It took about six weeks to get patients into hospital. Since it was impossible to wait, it was essential to use an ambulatory system. He was treating such patients with 600,000 units penicillin in peanut oil-beeswax for ten days (Sundays excluded), together with 480 mg. of mapharsen (60 mg. every other day), together with 2,400 mg. bismuth (0.2 g. on the first and every third day during the penicillin-arsenic course, thereafter once a week until completion). He had so far treated privately about sixty six such patients, with no failures. However, he was certain that there would be the failure rate of about 20 to 35 per cent. which one had come to expect. The present feeling, instigated by the statisticians, was that it was unwise to draw conclusions as to the effect of any given treatment system in patients with early syphilis without at least 1,000 cases to begin with. The losses from attrition were such that when one started with 1,000 patients it was unlikely that one would be able to follow more than 100 for ten years. It was essential, therefore, in the statistical estimation of such material, to use the actuarial method of life tables, since otherwise one got a wholly false statistical picture.

Dr. Forgan asked whether there had been any experience with a larger total dosage of penicillin in an aqueous solution that 2.4 million units. Dr. Moore said that they had had many. Among the forty odd treatment schemes which had been used there were a number with 4.8 million units, a few with 9.6 million units. In this connexion, they stumbled on a fact which might be considered to confirm a tentative finding of the experimental laboratory (in infections other than syphilis) that too much penicillin may be harmful. For example, comparing two series of patients, one treated with 2.4 million units in seven and a half days, and the other treated with 4.8 million units in fifteen days, the results were not so good in the latter. The observation is not yet statistically significant, but there were certain straws in the wind which indicated that with this therapeutic agent too much might be worse than the optimum. It was desirable to try to find out what was just enough.

As to Dr. Forgan's question about negroes, the only chart he showed in which white males were separated out from white females and coloured males and females was that dealing with duration of infection. White males were selected there because of the notoriously inaccurate memory of the average coloured male.

With regard to Dr. Nabarro's remarks, he would emphasize that the American material dealing with prenatal treatment had been based on that group of people in which the congenital infection would be most likely to occur. In women with primary and secondary syphilis the morbidity and mortality in infants, if the mothers were untreated, was 95 per cent.; if the mothers were treated with penicillin it was reduced to somewhere between 1 and 2 per cent., indicating that it had been possible to reduce the incidence of congenital syphilis almost to the vanishing point. For this one state of syphilitic infection, at any rate, all other methods of treatment should be abandoned and complete reliance placed on penicillin administered to pregnant women. The results were equally good when the mothers were treated late.