A DISCUSSION ON PENICILLIN THERAPY IN VENEREAL DISEASES IN WOMEN*

Dr. G. L. M. McElligott (the President) said that Dr. Eva Gallagher was to have opened the discussion but that she unfortunately could not be present. He felt that this subject was so important that the discussion on it should still take place, and he hoped members would give their experiences not only of the treatment of gonorrhoea but also of syphilis.

DR. MARY MICHAEL SHAW

Dr. Mary Michael Shaw said that up to date she had treated with penicillin about 100 women suffering from syphilis. The cases were not selected; some were not acute but had been given penicillin with the object of getting specimens of blood in order to ascertain the blood level of penicillin. Her results were not of any great value because she had not given penicillin by itself; every patient had also had arsenic or bismuth unless there was some contraindication. Only one or two patients had had penicillin and nothing else, and in those the results were dramatic. An adult congenital syphilitic improved greatly; and, in an old lady aged 70, a gummatous ulcer on the leg healed very quickly. She had seen 2 cases of severe urticaria, in 6 other cases out of the 100 there had been a local urticarial rash.

Dr. Shaw thought there was so little advantage to be gained from penicillin for gonorrhoea in women that she did not give it, unless there was a complication. Nobody had been bold enough to reduce, the stringency of the tests of cure. If women patients were to be kept under observation for 3 months, only 4 days would be saved by giving penicillin as opposed to a sulphonamide—at least the patients might become non-infective 4 days earlier—but as a rule any spread of infection took place before patients attended the clinic. Very few women went out of the clinic and knowingly infected other people.

Penicillin had been given to about 60 cases of gonorrhoea in women in whom a complication such as arthritis or some pelvic inflammation was present. There had been no ill-effects and the results had been surprisingly good. She had not had the experience of treating a frankly congenital syphilitic child with penicillin. Most of the babies had been born in the hospital, and the mothers had had full treatment during pregnancy with penicillin plus arsenic or bismuth.

DR. JEAN MORTON

Dr. Jean Morton said that in the Royal Air Force Medical Service 8 cases of secondary syphilis in women had been treated with 2,400,000 units of penicillin; 5 were followed up for 1 year, and 3 for 18 months. There were no failures amongst the 8 cases. A second group of 8 cases, 6 with secondary syphilis, and 2 with early latent syphilis, was given 2,400,000 units of penicillin combined with N.A.B., 0.3 g., given twice weekly, plus bismuthyl 0.2 g., given once weekly for a period of 6 weeks. Three patients had been under observation for 6 months, 3 for 9 months and 2 for 12 months. There were no failures in this group. A third group of 7 cases, all with secondary syphilis, had been given 4,000,000 units of penicillin plus a total of 3.6 g. of N.A.B. and 1.2 g. of bismuthyl. All 7 cases were followed up for 6 months with success. Her impression about giving penicillin alone was that the reactions were as frequent as when arsenic was given alone. There was no case of dermatitis, but there was 1 case of oedema with urticaria. When extensive lesions were accompanied with toxicity the improvement in the patients' conditions was more rapid when they were given penicillin alone than when they were given arsenic alone. When complications of gonorrhoea were present, such as arthritis or salpingitis, she thought that improvement in the clinical condition was more rapid with penicillin than with sulphonamides. A woman with marked arthritis of the elbow joint was given 300,000 units of penicillin, 10 injections of 30,000 units 3-hourly for 30 hours. The day after completion of treatment she could move her arm, and on the third day after completion she was able to do her hair.

Dr. Morton said she did not give penicillin in cases of gonorrhoea until the report of the serological test for syphilis had been received; in the meantime she carried on with sulphonamides.

DR. ROBERT LEES

Dr. Robert Lees said he had read in a medical journal that penicillin was liable to cause abortion in pregnant women. He had never seen such a case though he had now treated many pregnant women.

He had observed some cases of interest. One was a boy of 18 months who was referred to the dermatologist with an extensive eruption around the mouth. At first this was thought to be a congenital syphilitic lesion, but it was proved that the remainder of the family were normal, and the mother attributed the infection to a nursemaid. The child made a rapid and satisfactory recovery with penicillin. Another child had extremely gross congenital syphilis such as he had never before seen. All the classical signs were present, with a pustulous eruption on the palms and soles, and laryngitis, and a café-au-lait colour. The

*This discussion took place at the meeting of the Medical Society for the Study of Venereal Diseases, on June 29, 1944.
child was very much under weight and had a large liver and spleen, but, after treatment with penicillin by injection, had prospered and was gaining weight rapidly. The bullae had disappeared, and the child was doing better than he would have expected under any other system of treatment.

In a third case the mother had been treated, during pregnancy, with penicillin, 2-4 mega units; she was confined somewhat prematurely, and the baby weighed 1½ to 2 lb. It was a puny child and made little or no progress during the first 4 weeks of its life. There was so much doubt whether it would survive that it was decided not to give penicillin by injection, but penicillin was added to its feeds. From that moment the child began to gain weight and thrive. Unfortunately the nurses were unable to collect the baby's urine, so it was not known how much was excreted. Treatment was continued for 14 days. The dosage was double the amount usually given by injection, and 2,000 units was given 3-hourly. The child was under observation and was still thriving and gaining weight. It had not been given any other treatment. It had a negative blood test at birth.

The speaker wished that an obstetrician would give a dose of penicillin in cases in which a Cesarean section was about to be performed, so that after operation the concentration of penicillin in the maternal and fetal blood could be compared. He had read various American reports which were not very conclusive but which did indicate that penicillin got into the fetal circulation. He had been watching for a case of ophthalmia neonatorum in a child of a woman treated for gonorrhoea with penicillin, but up to the present had not seen such a case.

**DR. BETTY WALKER**

Dr. Betty Walker agreed with what Dr. Morton had said regarding gonorrhoea. Over 100 cases had been treated since Jan. 1, and there had been 6 relapses. She was sure that infection in women cleared up more quickly with penicillin than with the sulphonamides, and that the complications recovered more quickly too.

With regard to syphilis, about 300 unselected cases had been treated—of latent, pregnant, early, and neuro-syphilis—and there had not been one severe reaction in any of them. The early cases had shown the same percentage of Herxheimer reactions as with arsenic. All these women found their general well-being much increased, but she did not know whether this was the psychological effect of knowing that they had had penicillin, or the effect of the drug itself. About 30 cases of syphilis had been treated during pregnancy; all who had arsenic or bismuth also, so that she could not say what the results of penicillin alone really were; in any case it was too early. Thirteen infants had been born of women who had had penicillin and one course of arsenic; all were negative to the Wassermann test and had remained negative. None of them had yet reached the age of 6 months, so that it was still too early to form a conclusion. A midwife in a hostel for delinquent women with venereal disease had assured her that in an experience of 20 years the children born of the women who had had penicillin were much stronger than those who had been treated with arsenic alone. The infant which Dr. Lees had mentioned weighed 2¾ lb. at birth; it was now 8 weeks old and weighed 6½ lb., an increase which seemed miraculous.

**DR. MARINKOVITCH**

Dr. Marinkovitch said that since the title of the discussion was announced in September, 1945, he had taken special interest in this subject and had treated 40 pregnant patients with penicillin. All the cases were in the primary or secondary stage of syphilis, and all were given arsenic and bismuth. It was difficult to talk about final results but he certainly had not seen a baby with a positive Wassermann reaction and clinical symptoms born to any one of the 40 patients who had been treated. He thought that all mothers in the primary stage of syphilis should be treated with penicillin, as pregnant women in the secondary stage took a longer time to achieve negative serological tests. He had observed the tonic effect of penicillin in female as well as male patients. He had been impressed by the effect of the combined arsenic and penicillin treatment in pregnant women, and had not seen an abortion due to this treatment. He had treated three infants with penicillin alone, with the most excellent clinical results.

With regard to gonorrhea in women, the clinical results were not so dramatic as they had been in the early days of sulphonamide therapy. On microscopic examination of the urethral and cervical pus in such patients, numerous pus cells were seen but no gonococci. With regard to the treatment of gonococcal complications, his impression was that the results of penicillin therapy were not achieved rapidly. He had treated a man with synovitis of the knee and irtis with penicillin but with poor results, and finally had to give him a T.A.B. vaccine intravenously to achieve cure.

**DR. JAMES MARSHALL**

Dr. James Marshall did not recall that any contributor to the discussion had mentioned treatment of syphilis with penicillin alone. Just a year ago Major Laird and he disclosed that they were using a combined treatment, and they were frowned upon and told that their technique was bad and that if they had given their penicillin properly they would have cured syphilis. He wondered what had brought the change of heart. As far as the treatment of syphilis was concerned, in his clinic he now gave for primary syphilis 2,400,000 units of penicillin in aqueous solution, or 3,000,000 units in oil-wax suspension; combined with which he gave a 10-week course of arsenic and bismuth, either as neoarsphenamine once weekly, or arsenoxide twice weekly. For sero-positive and secondary syphilis, after one or two failures with the above treatment he had given the same amount of penicillin plus two courses of arsenic and bismuth, a total of 24 weeks' treatment.
He could not give any results, because this method had only been used for about 12 months.

Nearly half a dozen women during pregnancy with penicillin and arsenic, and 4 had had their babies. The blood tests at 6 weeks after birth in the children had been negative in all cases and they had shown no clinical signs of syphilis.

Penicillin was a great advance on the sulphonamides in the treatment of gonorrhoea; first in the percentage of cases which were cured by one course of treatment, and secondly in the fact that the treatment could be completed in every case as there was no trouble from intolerance of the drug. It surprised him to hear Dr. Mary Michael Shaw say that she did not use penicillin in her cases.

**DR. HEYWOOD**

Dr. Heywood apologized for having no statistical figures to support the clinical impressions of his own experience at Newcastle. For the treatment of gonorrhoea, both males and females, a variety of methods with penicillin had been tried. All gonorrhoea cases were treated with penicillin immediately on diagnosis. He began by using 100,000 units in an aqueous solution spread out over 15 hours, which required the keeping of the patient in hospital for that period of time. With that treatment, in the first series of nearly 100 cases, there had been no failures. In order to reduce the period during which the patients were kept at the hospital or clinic, the total dose was increased to 150,000 units spread over 8 hours. With that schedule there was a very high proportion of successes, and, of 3 cases that had failed, 2 responded to a second course. The third patient responded neither to a second, third, nor fourth course of penicillin, nor to sulphonamide, and eventually had to have fever treatment.

Using penicillin in an oil-wax suspension, according to the recommendations of the Ministry of Health, 200,000 units were given, but this had temporarily been increased to 250,000 for ease of administration. In women there had not been any reliance on the smear, which was difficult to distinguish between a relapse and a reinfection. In general the patients' histories were unreliable, and even if they admitted re-exposure to infection there was no evidence that they were reinfected. His impression was that females were cured by the first dose of penicillin, an impression borne out by biological tests, but this was so much at variance with his experience with male patients that he thought there was possibly something wrong with the follow-up methods in the female cases.

He wished to raise the question of diagnosis in suspected gonorrhoea. This was a problem which arose under Regulation 33 B. A woman was named as a possible source of infection, and she was either persuaded or compelled to attend a special practitioner or a clinic; it then became the medical officer's task to decide whether she had gonorrhoea. It was a real problem to decide what tests and how many to employ before discharging her as free from infection. Formerly, at Newcastle, a blood test and three consecutive smears were taken, and if these were negative the patient was discharged; but since they began to get contacts under 33 B so many female patients had been seen in whom gonococci could not be detected in the first, second, or even in a sixth smear, that it seemed there must be a longer time for investigation and a more detailed follow-up. He had heard of contacts under 33 B being discharged on the strength of one smear, which seemed highly unsatisfactory.

Salpingitis in women had been miraculously cured by penicillin, but Bartholinitis seemed to be less rapidly cured with penicillin than with the sulphonamides. The results in gonococcal vulvo-vaginitis were disappointing.

Dr. Heywood had had only four beds available to women with syphilis for 1,000,000 inhabitants, a number entirely inadequate for the treatment of patients with penicillin by 3-hourly injections. The situation had, however, been helped by the issue of the oil-wax suspension of penicillin. He was using penicillin with arsenic and bismuth. In such cases there had not been any serological or clinical relapses, and some of the patients had been under observation for over 12 months. A small number of early congenital syphilitic children had been treated, but the response was not as dramatic as had been hoped. His impression was that such patients treated with arsenic and bismuth healed more rapidly than the cases treated with penicillin.

**DR. W. NEVILLE MASCALL**

Dr. W. Neville Mascall said that he had investigated a small consecutive and unselected series of female patients, most of whom had been admitted to hospital for treatment. As far as penicillin treatment of gonorrhoea was concerned he had been disappointed. Out of 42 cases, 57 per cent. proved unsatisfactory in that gonococci had been present after a lapse of 7 days from the cessation of treatment. These cases had been tested in routine manner, namely, smears were taken from the urethra and cervix, cultures from the urethra, cervix, and vagina. He had not included the cases which merely showed a persistent gonococcal fixation test: the gonococci were actually either seen in smears or grown on cultures.

What did greatly surprise him was that in the series there were 12 patients treated for syphilis who had received 2,400,000 units of penicillin in hospital, and out of those 12, if he remembered rightly, 5 still had gonococci present at the end of the treatment, either in smears or cultures. One remarkable case was that of a girl with gonorrhoea who received 200,000 units of penicillin in ethyl oleate, and 7 days afterwards she developed a Bartholinitis from which the gonococci were cultivated.

Clinically the cases frequently showed little improvement after penicillin. When dealing with the vagina one was not generally dealing with a straightforward gonococcal infection. There were trichomonas and other organisms which penicillin would not touch, and it was no good saying,
"You are cured" as long as there was a discharge present, because the patients were not convinced. This appeared to be one of Dr. Marinovitch's problems. Patients had penicillin, and afterwards they might be cured of gonorrhoea; but they still had their symptoms and unless one did local treatment at the same time it was, from the patient's point of view, a waste of time to give them penicillin. He remembered when the sulphonamides came into use saying that they did not cure the discharges, and he said the same about penicillin.

In cases of vulvovaginitis he also obtained extraordinarily bad results. In this series there were only 3 children, but they all failed to respond to one course of penicillin. In fact one child had, altogether, 4 courses of penicillin, starting off with 150,000 units in water; she received 300,000 units in water but was still positive; she then received 300,000 units of penicillin in oil on two occasions and was still positive; finally the infection was cured by sulphanilamide. It might be suggested that she was being reinjected, but all the other members of the family had been examined and not one was positive, so that reinfection could be completely excluded. The other 2 cases failed to respond to a standard course of penicillin given in divided doses, which he thought the best method of administration.

He had been disappointed in the treatment of gonorrhoea with a single injection of penicillin in oil. He was sure that if the penicillin were spread over a longer period of time better results would be obtained. He was interested to hear from Dr. Curtis, who had recently returned from Germany, that the same difficulty was being experienced with vulvovaginitis and they had come to the conclusion that some other treatment besides penicillin was necessary. It was suggested that they should go back to oestrogen therapy as an adjuvant to penicillin.

Dr. Mascall said that his patients had been remarkably free of complications. He had seen a number of Herxheimer reactions in the treatment of syphilis but not more than one would expect. The question of swollen buttocks was a problem. He had treated a ballet dancer whose buttocks swelled to five times the normal size but finally settled down satisfactorily.

Since reporting 2 cases of early abortion during the treatment of patients with penicillin, he had read a lot about the action of penicillin on the uterus and had come to the conclusion that it was more marked in the non-pregnant than the pregnant uterus. The reaction was probably due not to the penicillin per se, but to certain impurities in the final product. At one time when giving penicillin in water he had thought that if the quantity of fluid in the injection was reduced there would be less pain, and he tried to reduce the amount to 2 c.c.m. for 200,000 units, but was alarmed at the number of collapses which his cases experienced. He reported this to the Ministry of Health, and they furnished him with some pure sodium penicillin, and on his using the same concentration these collapses did not occur.

Dr. S. M. Laird

Dr. S. M. Laird said that, of about 80 adult females suffering from gonorrhoea—of which 11 were treated with 100,000 units—6, or 55 per cent., were cured, in that they had negative smears and cultures after 3 consecutive periods following treatment. One case treated with 150,000 units was cured. Of 23 cases treated with 200,000 units, 12, or 52 per cent., were cured; of 24 cases treated with 300,000 units, 18, or 75 per cent., were cured; of 4 cases treated with 500,000 units, 2, or 50 per cent., were cured; of 9 treated with 600,000 units, 77 per cent. were cured, and 3 cases treated with 2,400,000 and a further 2 cases treated with 4,000,000 units were cured; so he concluded that it was worthless to use penicillin in the female in a dosage of under 300,000 units, and that probably somewhere about 500,000 or 600,000 units was the optimum dosage.

The limited experience he had had with penicillin in the treatment of the complications of gonorrhoea had disappointed him. In cases of salpingitis the acute symptoms responded well, but a considerable number of patients remained with positive cervical cultures and smears, and many of the failures in the cases mentioned occurred in patients who had had salpingitis. He was interested in what Dr. Mascall had said about vulvovaginitis. He had had the experience when he started his present duties, of inheriting 8 cases of vulvovaginitis which had been attending for 18 months and which had had frequent courses of a sulphonamide, and a number of courses of penicillin going up to as much as 800,000 units. He admitted them to hospital and gave them 1,200,000 units of penicillin, but without success. It was only after giving them oestrogen and following that up with small doses of penicillin that apparent cure had been effected. The surveillance period of these cases was about 4 months.

He had seen ophthalmia, not neonatorum, in one small child of about 2 years of age who also had vulvovaginitis, and although the response of the eye was disappointing, that of the vulvovaginitis was disappointing. He had only treated one baby with florid syphilis, and it had done extremely well. The twin of this baby was apparently healthy, and at 9 months still remained free from any symptoms of syphilis.

He had treated a number of cases of syphilis in pregnancy, and subsequently the babies appeared healthy and were serologically negative, but it was too early to draw conclusions. The response of tertiary lesions had been striking. The serological response in early syphilis was disappointing, it seemed to be slower than with arsenic and bismuth. His routine for the moment was 4,000,000 units of penicillin, together with 10 weekly injections of arsenic and bismuth, giving a total of 8-9 g.

Mr. Ambrose King

Mr. Ambrose King said that he, too, spoke from impressions and had no figures to present. In regard to the possible effect of penicillin on the uterus, causing menstrual irregularities and perhaps abortion or premature labour, he had seen
a large number of women treated with penicillin and had not heard any complaints of or noticed any of these complications.

On the question of the treatment of syphilis with penicillin, Dr. Marshall had mentioned an argument which took place a year ago, and spoke of a "change of heart"; as far as Mr. King was concerned he was not aware of any change of heart. The treatment of early syphilis with 2,400,000 units of penicillin alone had produced excellent results, and none of the figures published so far had served to correct that impression. Until a large number of these case records were analysed it was unsafe to draw conclusions. It had been said that 85 per cent. of patients with early syphilis would get well however badly treated, and the other 15 per cent. would give trouble however well they were treated. Perhaps the terms of this statement were too general, but it contained some truth; and it was still not established that adding more and more arsenic or bismuth to the treatment with penicillin would reduce the number of resistant cases.

Mr. King found it difficult to share the general optimism regarding treatment of gonorrhoea in the female with penicillin. He had had an opportunity of following most of the resistant cases of acute infection which Dr. Mascall had mentioned, and it was a fact that a percentage of cases treated with a large amount of penicillin failed to achieve bacteriological cure. He had been disappointed in the results in chronic infections also, because, although bacteriological cure was apparently achieved, many of these patients showed evidence of residual infection, such as chronic cervicitis, and symptoms and signs of pelvic infection. Pelvic infections, when acute, often responded well to penicillin, but many of these patients were seen afterwards with subacute relapses of their pelvic condition, and he doubted whether a substantial proportion of permanent cures was achieved by penicillin. Similarly with the metastatic infections of gonorrhoea, such as arthritis, the relief of immediate symptoms, such as pain and swelling, was sometimes satisfactory; but the end results were disappointing, and he felt strongly that most of these patients required the addition of some form of fever therapy in order to achieve lasting results.

Brigadier T. E. Osmond

Brigadier T. E. Osmond suggested that what had been said during the discussion was a great tribute to Dr. Orpwood Price. The Whitechapel Clinic had had poorer results than most people; in his view the more experienced pathologists would show up the failures better than the less experienced. The other point he would mention was the account in the *Journal of the American Medical Association* of a co-operative group which had been assessing penicillin and which had come to the conclusion that the present penicillin, which consisted of four factors, F, X, G, and K, contained more K, which was relatively ineffective, apparently because it was so rapidly destroyed in the body. The group proved conclusively that the results produced in syphilis up to May, 1944, were far better than the results since. It was interesting to note that they were now recommending for relapsed cases arsenic and bismuth in addition to penicillin—a method which had been used in this country for at least a year.

Dr. David Nabarro

Dr. David Nabarro said that among the several points brought forward one of the most interesting was that pregnant women could be treated with penicillin alone and their children be born healthy. He thought it a very important observation because it did away with the risks of arsenical treatment, which were generally given as a reason against the treatment of all positively-reacting pregnant mothers. The point mentioned by Brigadier Osmond, that the more penicillin was refined the less effective it became, was disconcerting; either they would have to revert to the use of impure penicillin, or find a better fraction of penicillin and use that, alone or combined with arsenic and bismuth.

In Dr. Nabarro's view there was still too much congenital syphilis in existence. They knew how to prevent it, and it was a disgrace that the disease still occurred. He went to the Hospital for Sick Children at Great Ormond Street, London, every Saturday, and frequently he was asked to look at a case of congenital syphilis. It had been found advisable, because of the shock reactions which sometimes occurred, to begin the treatment with smaller doses than were usually recommended; and he thought that treatment should be continued for at least 18 to 21 days. The total dosage, 170,000 units (Bodian, *Proc. roy. Soc. Med.*, Aug., 1945, p. 572), should be spread out over 2½ to 3 weeks.

In American literature there had been several references to penicillin giving rise to abortion. Ingraham and his co-workers in America had recently again suggested that it has this effect. Goodwin and Moore, on the other hand, concluded that they had not seen any case of it. Dr. Nabarro thought it must have been a coincidence that an infant did well with penicillin by mouth, because he would have thought the penicillin would be destroyed in the stomach.

When he was in charge of the clinic at the Hospital for Sick Children, Great Ormond Street, he treated many of the children with bismuth alone, and he found that one course of 12 injections of bismuth made the Wassermann reaction negative. He did not stop at that point, but repeated the courses of bismuth injections, and the patients seemed to have done well. He believed bismuth was a very valuable drug in syphilis.

To Dr. Nabarro's question whether lumbar punctures had been carried out on the cases which Dr. Morton had said were cured of syphilis with penicillin, Dr. Morton said yes. Dr. Nabarro said that he was constantly advising caution in claiming for penicillin more than it was capable of doing, and he thought we must wait at least 10 years before saying that a patient was probably clear of the disease.
LT.-COL. R. R. WILCOX

Lt.-Col. R. R. Willcox understood that the new 'drug,' Benadryl, was now coming into use in this country. In the United States this drug was showing very promising results in the treatment of urticaria occurring during penicillin therapy. Penicillin was also very effective in the treatment of secondary yaws. As far as the British Army was concerned there were published figures available for early syphilis showing that when 2,400,000 units of penicillin by itself were used there was an 8 per cent. relapse rate at 6 months. It was hoped that later figures would soon be available.

Mr. King asked whether it was not a fact that the published figures of 6 months' results were on 270 patients and not on the many thousands treated.

Col. Wilcox replied that the figure 270 referred only to those cases which it had been found possible to follow for 6 months at the time the particular estimate had been made. It had been drawn from many times that number actually treated. Such research in the Services was hampered by demobilization both of doctors and patients, but the Army was pursuing the investigations and it was hoped to have available further interesting figures shortly. The reference to the American article made by Brigadier Osmond was of great importance and might explain the differences of opinion between members as to the optimum dose of penicillin in the treatment of early syphilis. The article referred to information which came to light in America within a week of the United States Public Health Service conference on penicillin in syphilis held in Washington on Feb. 7-8, 1946. This was that laboratory experiments had shown that the K fraction of penicillin was ten times less effective in rabbit syphilis than penicillin G; furthermore that recently the commercial penicillins had contained greater and greater proportions of penicillin K. A later analysis of results had shown a gradual decline in the efficacy of commercial penicillin since 1944. It would be interesting to know if similar factors were operating in this country.

DR. V. E. LLOYD

Dr. V. E. Lloyd thought that the change in the efficacy of penicillin in America corresponded to a change in the method of manufacture. The deep tank method of production seemed to have produced a penicillin which did not give such good results in syphilis. The recent availability of penicillin in this country had depended on production from the deep tank method and he, and no doubt others, were a little uneasy as to the value of present-day penicillin. He had been assured by a representative of one of the manufacturers in Great Britain that the penicillin they produced contained very little penicillin K. It was penicillin K which had appeared in increased quantity in the American "deep tank" penicillin, and which was reputed to be of no value in syphilis. He had no doubt that others like himself were apprehensive of this situation and would like to see it cleared up. Perhaps the manufacturers would make some combined statement in the medical press on the present constitution of British-made penicillin.

There were several points in the discussion which had interested him. One was the account given by Dr. Lees of the infant who was treated by the addition of penicillin to its feeds. Dr. Lees seemed a little surprised at the excellent results, and further scepticism has been forthcoming in the discussion; but personally he thought it was an admirable way of treating a premature or recently-born syphilitic infant. There had been some work recently published which showed that the absorption of penicillin from the very young infant's stomach was very high, and that the blood level was adequate. In a few years it was likely that the treatment of very young infants with congenital syphilis would be by mouth or by the inhalation method by which penicillin was also absorbed very rapidly.

They had to think not only in terms of dosage of penicillin or method of administration, but also in terms of the relative accessibility of the various tissues of the body. A case of iritis in which the results were poor, but that was what one would expect. The degree of penetration of penicillin into the aqueous and vitreous fluids of the eye was very slight; it was almost impossible to get more than a trace of penicillin into the eye by whatever method it was given. There was some hope that increased accessibility into the eye might be effected by the therapeutic production of increased vascularity in the eye. There was a pointer to this in the treatment of interstitial keratitis where the results of treatment with arsenic were better when it was given in the stage of high ocular vascularity. The treatment of joint disorders also was not very successful. The amount of penicillin reaching the synovial cavity was very small, and already physicians had started to treat arthritis by aspirating the joint fluid and then inserting the penicillin. These limitations had to be borne in mind when assessing the value of penicillin.

MAJOR IRENE HOWARTH

Major Irene Howarth said that at her treatment centre, 30 cases of syphilis had been treated with 2,400,000 units of penicillin. There was considerable difficulty in following the patients up, owing to demobilization and also because many had left the area and attended other centres. One patient had been followed up for 18 months, 1 for 12 months, 3 for 6 months and 12 for 2 to 5 months, and all so far were satisfactory. More recently 28 cases of syphilis had been treated with 4,000,000 units and so far all attending the treatment centre were satisfactory though they had not been followed up for very long. These two series included 4 pregnant women who had had no disturbance of the pregnancy. These 4 patients were given arsenic and bismuth injections weekly after the penicillin course.

*Henderson, J. L., and McAdam, I. W. J. 1946. Lancet, 1, 922
One of the 4 cases of double infection treated with 2,400,000 units of penicillin still harboured gonococci at the end of the course; subsequently, after a course of sulphathiazole, all smears and cultures were negative. One mucocutaneous relapse was seen which had been treated at another centre in July, 1945, with penicillin (2,400,000 units) for a primary sore of the lip. The Kahn tests were negative in October and December, 1945; but in February of this year the Kahn was positive (20 units). Mucous patches were present in the mouth and there were many small vulval ulcers, the serum from which contained T. pallidum. This case was treated with penicillin 4,000,000 units and intensive mapharside therapy, and so far the result was satisfactory.

Sixty consecutive cases of gonorrhoea were treated with 100,000 units of penicillin, and of these 19 had passed their final test of cure. There were 7 known relapses—3 positive before discharge from hospital, 3 positive at the first surveillance tests, and 1 positive at the third surveillance test; 34 cases had not yet completed surveillance or had been demolished. More recently 200,000 units of penicillin had been used for gonorrhoea and none of the cases had yet completed surveillance, but all were negative immediately after treatment. Just over 50 per cent. of her cases of gonorrhoea also had trichomonas vaginitis. The only complications of treatment with penicillin which she had encountered were 2 cases with intense urticaria and one girl who had extremely severe dysmenorrhea.

**Dr. Letitia Fairfield**

Dr. Letitia Fairfield said that the last speaker and others had raised in her mind a problem which had not been mentioned and which was not directly clinical, but which seemed to be of considerable importance. In connexion with the planning for a national health service, she found that there was a tendency to assume that the social problem of infectivity, especially in women, was already solved by sulphonamides and penicillin, and that it was unnecessary to have any provision for what she might call the preventive type. In London and elsewhere, hostels had been established where women who were likely to expose themselves and others to the infection were encouraged to remain, and where attention was paid not only to guarding them during the period of possible relapse but also to making a real endeavour to rehabilitate them and get them to adopt some other means of livelihood. She hoped that when members were being consulted on these matters they would remember these points; she felt that otherwise a very unfortunate position might arise, because there was widespread misunderstanding about the position which treatment of venereal disease had attained. She felt strongly that they could not yet rely on out-patient treatment only, and that the lay officials in whose hands their destinies so largely lay should not be encouraged to believe that out-patient treatment was adequate for the prevention and cure of venereal disease.

**Dr. Heywood**

Dr. Heywood said that, with regard to Mr. King's statement that he was satisfied with the penicillin treatment of early syphilis, he thought that Col. Pillsbury's second paper published in the United States recorded that secondary syphilis treated with penicillin also had an infectious relapse rate of over 20 per cent. Mr. King said he was referring to early syphilis generally. He did not say he was satisfied, but on comparison he still considered it to be good treatment.

Dr. Heywood said that, whatever might happen ultimately to patients treated with penicillin, a high infectious relapse rate was alarming from the public health point of view.

His impression was that there was a great deal of unrecognized congenital syphilis but that they were only dealing with the few cases which came to light fortuitously. This was a blot on the antenatal services of the country; it could be wiped out completely by proper antenatal treatment.

On the question of follow-up of female patients treated with penicillin for gonorrhoea, the treatment had been made so easy that the patients defaulted earlier than ever. In his experience the early default rate was greater now than it was before gonorrhoea was treated with penicillin, and also in his experience the administration of even a small dose of penicillin, 100,000 or 150,000 units, to a patient with gonorrhoea might delay the appearance of syphilis for as much as 3 months. The practice had been adopted that all patients must remain under observation for at least 6 months to make sure that concomitant syphilis had not been masked by the penicillin.

**Major Wordingham**

Major Wordingham spoke from the experience of a large number of male patients and to a lesser extent of female patients. He felt that the present tendency, to neglect local therapy and to give penicillin alone, was one of undertreatment. He treated all complicated cases of gonorrhoea in men with 150,000 units of penicillin together with 24 g. of sulphathiazole in 4 days. Female patients, whose cases were notoriously complicated and who often attended only when the condition was well advanced, were given 300,000 units combined with 24 g. of sulphathiazole.

Many venereologists would not face the fact that a large number of patients treated with a single or five multiple injections of penicillin alone, up to a total of 150,000 to 200,000 units, had a recurrent urethral or cervical discharge. They were not cured. Too often the cases were diagnosed as non-specific infections, when in fact they were relapses; he thought that this was due to inadequate initial therapy. They were deluding themselves in relying upon penicillin alone, especially in the male with complications and in every female patient, and this was also the experience of some of his civilian colleagues.

The routine treatment of syphilitic pregnant women, of whom he had seen many recently,
was 4 mega units of penicillin. For a fit woman he had combined this with 8 to 10 daily injections of 0.04 mg. of mapharsen together with 5 bi-weekly injections of 0.2 g. of bismuth. There had been no untoward reactions with this routine. The first baby had arrived and was perfectly healthy; the mother had had secondary syphilis.

In the treatment of early syphilis with 2.4 mega units of penicillin, the suggested relapse rate of 8 per cent. was a little conservative; his experience would indicate a 20 per cent. relapse rate within 6 to 9 months. No dangerous complications had been encountered during combined treatment of penicillin and intensive therapy with mapharsen, even with that treatment he had seen 4 relapses and, therefore, he thought that primary sero-positive cases would do much better if bismuth was also given. In the Army it was possible to achieve by with 2.4 to 4.0 mega units of penicillin and 0.4 to 0.6 g. of mapharsen, together with 1 g. of bismuth. In civilian practice out patients could be treated with daily injections of the oil-wax preparation, slightly lower doses of mapharsen, and bi-weekly bismuth. From his observation of the reaction of the soldier to this routine he thought that most civilians should be able to follow their employment. The absence of severe complications, such as dermatitis and encephalopathy, made him wonder whether the penicillin counteracted the toxic effects of the mapharsen in any way.

Had the gonococcal complement fixation test any value now? He did find it valuable as a test of cure, and often it enabled him to decide whether a case was one of relapse or reinfection. He had recently found the test positive in the majority of the cases that had failed to respond to the single injection treatment.

Mr. King asked if he might make his point of view clear on the question of penicillin for early syphilis. He was not satisfied with the results with 2,400,000 units alone, and in his own patients he used arsenic and bismuth as well. At the same time there had not been a survey of a large number of cases which proved beyond question that the 2,400,000 units was unsatisfactory, and it was wrong to form ideas on a few scattered impressions, or on the unsatisfactory experiences of a few people with few cases. It was necessary to have an investigation on a large number of cases.

Dr. Burgess

Dr. Burgess supported contention that better results were obtained in the treatment of early syphilis by using penicillin together with arsenic and bismuth. He had been giving 500,000 units daily for 10 days with a full course of neoarsphenamine and bismuth, and so far he had not seen any relapses. There had been two cases of urticarial rashes, and one case developed acute angioneurotic oedema. In cases of gonorrhoea, better results were obtained by giving concurrent sulphathiazole, 25 g. in 5 days and an initial injection of 250,000 units of penicillin.

He also had had the experience reported by Dr. Marinkovitch, that the vaginal discharge did not clear up. Many patients said that the discharge was worse after penicillin. In his view most of these cases would be found to have a concurrent trichomonas infection, and unless this was treated also the results from the patient's point of view would be very poor. He did not know whether the penicillin encouraged the trichomonas, but he had found positive specimens more frequently after penicillin than before.

On the question of cultures it might be that the medium used was not so good as in other places, but he had never had a positive culture unless it had been grown in 8 per cent. carbon dioxide; plain cultures gave negative results. By using this method he had obtained many positive cultures where the smears had been negative.

Major Betty Walker

Major Betty Walker said that unless trichomonas infestation was treated simultaneously with gonorrhoea good results would not be obtained. She wondered whether the reason that some speakers did not attain good results was that the trichomonas vaginitis or concurrent cervicitis had not received local treatment at the same time.

Major Scott

Major Scott said that he had noticed that gonorrhoea patients treated by him had been returning 5 or 6 weeks after treatment by penicillin with considerable urethral discharge, in which pus cells, with gonococci and other organisms, were present. Further examination showed the presence of a hazy urine. A large proportion of men were failing their final tests of cure. Examination showed a great number of pus cells in the prostatic bead. He thought that it might be a wise procedure to examine the prostatic contents some 4 or 5 weeks after discharge from hospital, so that further treatment, if necessary, might be given at an early stage.

Major Scott had recently seen a case of secondary syphilis that had been treated in Germany some 3 months previously with 2,400,000 units of penicillin. The clinical condition had been little improved, and a florid maculo-papular eruption with associated laryngitis was still present.

With regard to gonorrhoea, he thought that possibly the best results he had seen were in cases in which penicillin had been combined with sulphathiazole. Abroad he had been using penicillin, 140,000 units, combined with 15 g. of sulphathiazole. On the first day the patient received 7 injections, each of 20,000 units of penicillin, together with 4, and thereafter 2 tablets of sulphathiazole. On the second day sulphathiazole was given alone, in 7 further doses of 2 tablets. He believed that this treatment gave a high rate of incidence of cure.

Dr. G. L. M. McElligott

Dr. G. L. M. McElligott (the President) thought the reason why penicillin had not been used alone in civilian practice was, first, shortage of beds and, secondly, unreliability and shortage of supply of drugs.
When evaluating treatment by penicillin and arsenic and bismuth, it was necessary to bear constantly in mind that a minimal amount of arsenic-bismuth treatment would cure many cases of early syphilis. Most would agree that about 5 g. of neoarsphenamine and 2 g. of bismuth in one course would cure between 60 and 70 per cent. of cases of early syphilis. They were told that 15 per cent. of all cases of early syphilis could not be cured, and it had to be borne in mind that 20 per cent. of cases of early syphilis, even if not treated, would ultimately “cure themselves,” which did not leave much margin for evaluating the penicillin. In all cases of syphilis, early or late, with the possible exception of advanced and gross cardiovascular syphilis, penicillin was indicated. He thought they must make up their minds to give it to all cases of syphilis in addition to any other treatment they felt the patient should have. The place of penicillin in the treatment of syphilis had not yet been determined and it would be a long time before it could be so determined, but it was a powerful anti-syphilitic drug, it was comparatively harmless, and why should it not be used?

With regard to gonorrhoea, the results which a great many of the speakers had reported were rather depressing. It might be that there was too much of penicillin K in the preparation, but that was not known. What was significant was that the dosage of penicillin seemed to be rising for the treatment of gonorrhoea. They used to talk about 100,000 units 18 months ago, and now they were talking about 300,000 units. It might be that the gonococcus was getting used to it, and now that it was likely that every case of tonsillitis would in future get a shot of penicillin from the doctor he thought they would have to watch for real trouble.

The follow-up of gonorrhoea cases was very important and he thought it should be more detailed even more than prolonged. During the first fortnight and three weeks they needed to see female patients almost every second day. The giving of a “few shots” of penicillin and saying, “Come back after the next period,” was inadvisable. After the first three weeks one had a good idea of what was going to happen. He thought that local treatment was necessary. Gonorrhoea in the female was a mixed infection. The infected and abraded cervix was in contact with a potentially septic vagina, and organisms which did not have the ability to penetrate healthy mucous membrane could flourish upon an unhealthy mucous membrane. The coincidental trichomonas infestation seemed to be getting more and more common, and his own practice was to advise a douche while giving the penicillin and for a week after, in the hope that such cervical discharge as was in the vagina would be washed away and the vagina would not be reinfected.

He thought that to give sulphonamides as well as penicillin was good practice, but he did not agree with treating cases initially with sulphonamides and only treating the failures with penicillin. The great point about penicillin was that one knew that the patient was getting the treatment; with sulphonamide treatment in women how often was regular medication carried out? The dosage of penicillin seemed to be arbitrary, but as far as women were concerned it was getting very near, if not up to, 300,000 units. He had seen 2 cases of inter-uterine bleeding in six months and one of these cases actually aborted.