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and help he has always given us, and the Sick Berth staff for their never-failing help and collaboration.

REFERENCES

DISCUSSION ON THE PRECEDING PAPERS

Brig. Osmond (the President) said that the two papers were some of the most interesting to which the Society had listened for a considerable time, and that he was glad to be the first to congratulate the two officers on the result which they had achieved. He was particularly interested in Surg. Lt. Cdr. Maitland’s explanation of the results in his cases. He had never been quite convinced by the usual explanation of the Herxheimer reaction, and Cdr. Maitland’s explanation might be the right one. As a point of interest, he would add that in the Army intensive treatment had been given in a much greater number of sero-negative primary than of sero-positive primary and secondary cases.

With regard to encephalopathy, Ransome (in a paper not yet published) had stated that the nursing of patients in Fowler’s position gave much better results than those obtained in the lying-down position.

As regards relapse rate, penicillin seemed to compare extremely well with intensive arsenic. Brig. Osmond thought that great care must be taken in diagnosing re-infections, because the more he thought about it, the more inclined he was to call the condition a relapse unless there was clear evidence of re-infection. As regards future therapy, such conditions should be treated as relapses.

If he might prophesy, it would be to say that most venereologists in the future would be using bismuth as well as intensive arsenic or penicillin. Penicillin acted in the same way as did the old “606”, by knocking out 99 per cent of the spirochaetes, but bismuth dealt with the odd 1 per cent. Toxic reactions were nearly all due to impurities, and if penicillin were made more pure there would probably be few toxic reactions. It was said that penicillin did not get into the cerebrospinal fluid, but it was carried to the brain and nerve tissues by the blood stream and might be expected to act nearly as well in cerebrospinal syphilis as in somatic syphilis.

With regard to the single daily dose method mentioned by Surg. Capt. Lloyd Jones, the facts that penicillin remained in the body so much longer when given in large doses, and that patients could be treated on an out-patient basis, were very encouraging.

Lt.-col. A. J. King said that he had listened with particular interest to the account of methods attempted in order to overcome the difficulties attendant upon the use of penicillin for the treatment of syphilis by multiple injection. He took it that the speakers would not regard this as more than a preliminary report; the whole investigation would be much more interesting and convincing if presented after a lapse of a year or two.

With regard to Cdr. Maitland’s point about the three stages of primary syphilis and the suggestion that upon these depend the amount of treatment given, the suggestion was interesting. Personally, however, he did not feel convinced, because this method seemed to leave out of consideration the personal idiosyncrasy of the patient and his ability to use the drug. It had always been the principle in the case of a disease such as syphilis to over-treat rather than under-treat; he thought, in view of the serious late manifestations, that it was a disease in which a little extra treatment might act as an insurance.

The President had raised a point regarding re-infections. It seemed clear to most people that recurring syphilis must be regarded as relapse until it was established by the most stringent criteria as re-infection.

Finally, Col. King thought that the necessity for treating syphilis on an ambulant basis in civil life was being exaggerated. If the patient had a respiratory infection, influenza or a severe cold, he had in most cases no difficulty in taking a week away from his work; in the case of a serious disease like syphilis, it seemed to him that it was purely a matter of education to convince the public as a whole that it was essential for that length of time away from work to be allowed if there was the chance of cure of so serious a condition within a short time.

Col. L. W. Harrison said that he had found the papers very provocative; he hoped that the authors would not think him too conservative if he criticized them a little. The idea of giving a single daily injection was most important; if it proved to be successful, it would solve many practical difficulties. The Ministry of Health had recently issued a circular in which the treatment recommended for syphilis included 60 injections of penicillin at 3-hourly intervals; he would watch for the results of the single daily dose method with interest and sympathy, but for the present he proposed to adhere to the multiple daily injection procedure.

On the question of re-infections, he agreed with the President and Col. King as to the danger of diagnosing as re-infections what were in fact relapses. During, or just after, the war of 1914-
1918, when he was a member of the Salvarsan Committee of the Medical Research Council, a paper was presented to the Council in which the authors recommended that all syphilitic patients in one of the Services should be treated only with neoarsphenamine. The authors relied for their case partly on a number of alleged re-infections, but from the details which were furnished he had no hesitation in pronouncing a number of them to be relapses. One must be extraordinarily careful before making a case to be one of re-infection and be one of the very rare cases. Capt. Lloyd Jones speak of a re-infection before the titre of the Wassermann reaction had dropped.

With regard to the classification into early, middle and late primary syphilis, he would agree with Col. King that it did not take into account the varying reactivity of the patients.

With regard to provocation of the disease by the treatment, surely the rise in the titre of the serum reaction of cases classed as middle primary was due to increased activity of the spirochaetes before they died. Did nobody believe in increased ante-mortem activity of such organisms? It was easy to demonstrate it in S. pallida, but it could be seen well in trypanosomes. If some trypanosomes were submitted to dark-ground examination with a pretty strong light, such as a Nernst lamp, it was possible to see enormously increased activity in them—quite different from the rather lazy movement seen under ordinary axial illumination—for a few minutes, and then the organisms just disintegrated, becoming unrecognizable.

Dr. V. E. Lloyd said that the matter of re-infection at a time when the titre of the serum was very high was of much interest and importance. At first sight one would think that it was very rarely possible for additional inoculation to take place at such a time, but experiments made by some Russian workers about 15 years ago seem to indicate such a possibility. These Russian workers investigated the reactivity of the skin to the introduction of spirochaetes in patients in various stages of syphilis. The inoculations were not often successful, but in some cases of tertiary and congenital syphilis, when a rich inoculum of spirochaetes into the skin was used, syphilitic lesions developed at the site of inoculation and occasionally also at other sites. In the late cases the response to inoculation was a lesion of a gummatous nature.

Similar experiments on the skin of patients in the earlier stages of syphilitic infection resulted, although rarely, in the appearance of a syphilitic papule. No doubt many of these experiments were made when the titre of the serum was very high. He thought that even when the titre was high re-infection might be a possibility, if the inoculum were very rich in spirochaetes.

Col. Harrison asked whether the inoculum was likely to be so rich in natural circumstances. Had Dr. Lloyd taken into account the fact that such reactions could be produced with dead spirochaetes?

Dr. Lloyd, in reply, said that he did not know whether or not that point was discussed in that particular report; to the best of his recollection, the description of the resultant lesion in the early latent cases was that of a secondary papule.

Lt.-col. R. Lees congratulated the authors on not forgetting the future adaptation of their work to civil practice. All medical men in the Forces were apt to develop their work on lines best suited to the present circumstances only; but the authors' work was continued and the patients followed up, it might have a tremendous influence.

Penicillin was adopted by the Central Mediterranean Forces from lst September 1944 onwards as the routine method of treatment of early syphilis. The total dosage was 2,000,000 units, divided into 100 injections of 20,000 units at 3-hourly intervals, and given intramuscularly. He had been favourably impressed by the clinical results; all the lesions disappeared quickly, spirochaetes were absent after the third injection and the primary and secondary lesions disappeared with great speed. The patients were discharged from hospital as quickly as under any other treatment. Serological reports were being collated, but at the time when he left Italy it had been too early to do anything more than make a very brief incomplete summary.

Every endeavour must be made to present as complete and detailed a study of these penicillin-treated groups as possible. The group which had been treated during September 1944 (about 350 cases) contained a very few patients in whom the original negative Kahn reaction had become positive within 3 months, and these were evidently cases of serological relapse. All the other cases which were sero-negative at the beginning of the treatment had remained negative. There was a large intermediate group of cases which had doubtful serological tests 3 months after treatment. The observation period was 6 months and until that period had elapsed results could not be quoted. There was one definite clinical relapse, with a recurrent genital chancre but negative serological tests, which occurred 3 months after treatment. The patient denied exposure and his case was accepted as a relapse. He was treated again with penicillin; spirochaetes disappeared and the lesion healed; he would be watched with very great care.

The side effects were not, as a rule, serious; but they were relatively frequent. Pyrexia of various degrees, malaise and herpes were often troublesome and mental confusion occasionally. Patients who had late primary syphilis almost all had toxic reactions. In many who had not shown early skin lesions an early macular eruption developed and lasted for about 24 hours. The later type of syphilide had a distinct increase in the size of the eruption, glands were more readily detected and there was quite obviously a clinical flare-up of the disease.

Col. Lees was impressed by the possibilities of penicillin treatment, but wished to emphasize that the matter was sub judice, and that the Forces were preparing a very careful mass follow-up system which would be a guide for the future. Like Col. King, he wished also to emphasize that
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it was not absolutely necessary to adopt the single dose technique for civil practice. It might be better to accept the necessity or desirability of putting the patients into hospital for 7-10 days, treating them as one would treat a patient with serious disease, and giving them a prolonged follow-up.

He wished to deprecate any rapid conclusion based upon a satisfactory serological report. He had seen many patients in the last 15 years with syphilitic lesions becoming active after prolonged latency and negative serology, and he was very reluctant to accept negative serological tests alone as proof of cure. These individuals must be kept under surveillance for a very long time. He hoped that the present clinical and serological follow-up being done in the Forces could be maintained for several years and for a high percentage of all cases treated, so that something of permanent value would be obtained.

Major Marshall said that he was most interested in Capt. Lloyd Jones’s results. They did not see eye to eye on the classification of syphilis, but that was a matter of opinion. Maj. Marshall felt that syphilis was a universal infection from its very early days and that it was not safe to assess the treatment from serological reactions only. When he was treating syphilis with penicillin and serological examinations were carried out from the beginning, he found that the activity of the spirochaetes was increased from about the sixth to the ninth hour after treatment had begun, and that after that they disappeared completely or became negative. He had had no experience with the single daily dose of penicillin.

It was too early to be definite with regard to the final outcome of the treatment with penicillin by the 60-injection method, but he had seen a fair number of cutaneous relapses after this form of treatment. He considered that the treatment of the future might be, as suggested by certain American workers, a combination of arsenoxide and penicillin.

Air Commodore McElligott congratulated the authors on having broken new ground. During the last 25 years syphilitic treatment had been fairly satisfactory—very satisfactory when the patients would allow it—with the combination of two substances: one drug, bismuth, which maintained a fairly constant blood level all the time and a compound, neoarsphenamine, which did not maintain anything like a constant blood level. In fact most of the neoarsphenamine had gone from the system long before the next injection took place, and the patient was left with a reserve of bismuth in his buttock to carry him on to the next injection.

The President had suggested the possibility of combining penicillin with bismuth; that was a very logical attitude to take in view of experience. Penicillin could not be compared accurately with neoarsphenamine. Most of the penicillin had gone within a few hours and most of the neoarsphenamine had gone within a few days. He felt that the combination of these two substances—it was known that penicillin was “very strong medicine” as far as the spirochaete was concerned—was well worth trying.

Another point which had been raised was the question of the possibly provocative effect of an injection of penicillin, or of any antisyphilitic substance, on the serology. He had always preferred to consider the rise in titre which sometimes occurred a few days after the first injection of neoarsphenamine as an indication that the formation of reagin had begun and that it could not be stopped immediately. This was admittedly a hypothetical explanation, but it was perhaps as good a one as was provocation.

Sqn.-lrd. Jean Morton said that if new methods were not tried out no one would be able to decide which was the best.

With regard to penicillin treatment, the patients’ lesions cleared up very quickly; the total dosage given was 2,400,000 units. The blood tests were becoming negative within the recognized period. Her experience of this line of treatment was as yet very limited.

Dr. W. N. Mascall said that the chief problem in the intensive treatment of out-patients was defaulting. He could foresee the same problem cropping up with penicillin treatment, because it was at present very difficult to persuade a patient to attend every day for 8 days.

The age incidence of venereal disease had fallen considerably and a large proportion of the patients were now between the ages of 16 and 20 years. They were totally irresponsible and would not go into hospital for treatment. Until there was some way of forcing them to do so, or of compelling them to take treatment, most of these rapid methods were doomed to failure. He also thought that it would be difficult for a married woman to leave her family for 8 days’ inpatient treatment with penicillin without any awkward questions being asked by relatives and friends.

Dr. Erskine was not convinced of the suitability of the single daily intravenous injection of penicillin. Neoarsphenamine injections given at weekly intervals did not exert a direct bacteriostatic effect, whereas with penicillin and sulphonamides the bacteriostatic action was the important factor. When using sulphonamides it was necessary to maintain a constant adequate blood concentration and there had been some drug resistance where this had not been achieved. He thought that penicillin worked in much the same way as did the sulphonamides. If penicillin were given once daily, allowing complete excretion before the next dose, would there not be a risk that penicillin-resistant strains of S. pallida might be produced in the same way as were the sulphonamide-resistant strains of gonococci? Was there any evidence of penicillin resistance developing in any of these cases?
Dr. Suchet, speaking from the bacteriological standpoint, said that experiments made so far proved that it was impossible to make any organism which was susceptible to penicillin, penicillin-fast. There was no reason to believe that penicillin acted in the same way as did the sulphonamides, so that the experiment suggested by Lloyd Jones and Maitland was to be recommended.

One matter which was not known was the clinical level of penicillin which was efficient. All efforts to determine this had failed, and the level which was used and which was found as the result of bacteriological examination—and the blood level of penicillin could be determined only by bacteriological examination—was empirical. Investigation in the United States of America had shown that levels undetectable in the blood by means of bacteriological examination were nevertheless clinically effective and efficient. It would seem that to give these massive doses of penicillin, although the excretion was completed after 8-10 hours, would ensure that for many hours penicillin was present, although undetectable, and was doing some good in the body.

Work was being done on similar lines in other diseases and similarly good results were being obtained. It would seem that these 3-hourly or 4-hourly injections were given because a high blood level was expected, but that it might be unnecessary with penicillin.

Dr. B. Buckley Sharp agreed with Surg. Capt. Lloyd Jones on the advisability of providing a form of ambulatory treatment for syphilitic cases in civil life. It was all very well to say that the public must be educated into realizing that the disease was serious; but unfortunately absence from work entailed certification and inquiry from the patient's friends and relatives, and unless the public could be educated to believe that venereal disease was not a social stigma, he did not think that many civil patients would agree to go into hospital for a week or so for treatment.

Dr. C. P. Heywood said with regard to Dr. Lloyd's account of the Russian experiments, that the distinction was between re-infection and super-infection; Dr. Lloyd had described a super-infection rather than a re-infection.

Surg. Lieut. Cdr. F. G. Maitland, in reply, said that a different dosage was given to each of the 3 separate groups of primary syphilis patients who were undergoing intensive treatment with arsenicals or with penicillin. He had recognized two types of jaundice and he thanked Prof. Beattie and Maj. Marshall for their collaboration and help in the treatment of this complication.

On the matter of late absorption and excretion of penicillin, there had been reports from the United States of America of methods intended to encourage these; but a few trials with wax and oil had not been satisfactory so far. In a conversation he had had with Sir Alexander Fleming, the latter had said he had had little experience with the oil and beeswax, as it was a quite recent innovation. Another method suggested was to delay the passage through the kidney; but the promised drug had not arrived and so experimental work could not be carried out. With regard to the categories, he was pleased that this point had aroused interest.

Surg. Capt. T. R. Lloyd Jones, in reply to Col. Harrison, said that he hoped that his particular method of treatment would be of great help to the civil community; both Col. Harrison and Dr. Letitia Fairfield had referred in previous meetings to the difficulty of obtaining beds for venereal diseases patients, and it was felt that the method described would be a solution of this problem. When Mahoney started the treatment of syphilis with penicillin, there was doubt concerning its efficiency, but this doubt had been removed; there might be doubt also about this new method of treatment with penicillin, but its results so far had been encouraging and time would prove its worth.

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**THE SUITABILITY OF KAHN ANTIGENS FOR THE TECHNIQUE USED IN THE CITOCHOL REACTION**


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The present investigations have been carried out in order to discover whether or not Kahn antigens may be used in a similar manner to that employed for the citochol reaction (or Sachs-Witebsky reaction). Both antigens are distinguished by the high concentration of lipoids; they differ in the mode of preparation.

Kahn antigen is obtained by extraction of dried beef heart powder with alcohol after preliminary treatment with ether (Kahn 1 and 2), whereas wet minced beef heart is extracted for the citochol antigen with alcohol, the crude extract being then concentrated by evaporation (Sachs and Witebsky 3). The sensitivity of the citochol reaction is secured by diluting the cholesterolized extract with 3 per cent sodium chloride solution in two stages (Sachs and Witebsky 3). First, one part of the extract is quickly mixed with two parts of 3 per cent sodium chloride solution, then 9 further parts of the latter are rapidly added after 5 minutes' interval. Thus a twelve-fold dilution is obtained, which is mixed with equal amounts of undiluted serum for the performance of the test.