SULPHONAMIDE THERAPY OF GONORRHOEA IN THE MALE

part for vitamin B₁ deficiency in producing the liver atrophy which occurs during arsenical treatment. It is possible that the same factors of arsenic and vitamin B₁ deficiency may bring about the other serious arsenical toxaemias by affecting other tissues, for instance skin or bone marrow.

The intensive treatment was carried out under the direction of Brig. R. Lees, Consultant Venereologist, M.E.F., whose help and guidance is gratefully acknowledged.

Thanks are due to Major A. L. Williams, Capt. A. D. S. Cameron, Capt. W. R. S. Cowe and Capt. F. Lancely, R.A.M.C., who assisted at various times during the period of treatment; to Major Cook and Major Amies, R.A.M.C., for pathological investigation; to Capt. Morgan, R.A.M.C., for his excellent post-mortem report in Case 2; finally to Major C. Vaillant, R.A.M.C., for his cooperation in the medical care of the cases of encephalopathy which developed. Without their help this work would have been impossible.

SULPHONAMIDE THERAPY OF GONORRHOEA IN THE MALE

REVIEW OF FOUR YEARS' EXPERIENCE*


The unrestrained ardour and enthusiasm which inevitably hamper assessment of the power of new and valuable remedies—which only restriction of supply has prevented from engulfing early judgment of the new drug, penicillin—have become a matter of ancient history with regard to the sulphonamide therapy of gonorrhoea. Early claims of success in 90 to 100 per cent of cases, often based on very small experience, have been relegated to the forgotten and forgiven past.

Early work with sulphonamides

The extensive literature which has accumulated on this subject makes a full survey impossible. It is of interest however to quote the experiences in the last five years of some workers in Great Britain who have recorded their results from the use of sulphapyridine.

In 1939 at a meeting of this Society Cokkinis claimed that 77 per cent of cases treated in the first week of the disease and 85 per cent treated in the second week were cured, with a late relapse rate of 9 per cent. At the same meeting one of us (King) claimed that in over 90 per cent of 300 cases signs and symptoms had disappeared in less than three weeks. 250 of these cases had irrigations of the posterior urethra, which did not materially affect the results.

In 1940 Prebble gave his results in two series of cases. In the first series, 65 cases were treated with 3 grammes of sulphapyridine daily for 6 days with a cure rate of 57 per cent. A second series of 246 cases was treated with 3 grammes daily for 7 days and 1½ grammes daily for 7 days, with irrigations in most cases. Of these there was "real cure" in 66·4 per cent and "apparent cure" in 24 per cent. Mackinnon in the same year stated that the following scheme of treatment was likely to give a 100 per cent rate of cure. In the first week 1·5 grammes were given daily with urethral irrigations; in the second week 0·75 gramme daily with urethral irrigations and in the third week urethral irrigations only. He admitted a 5·5 per cent relapse rate after provocation.

Sommerville in 1941 treated 300 cases with 2 grammes daily for 7 days followed by irrigations for 2 weeks. There were only 2 failures (0·7 per cent) and relapse in 6·7 per cent. He considered that these results served to prove his contention that large doses of the drug were not necessary—with all due deference to those who believed in and employed massive or intensive dosage. MacKenna gave 22 grammes in 48 hours followed by irrigations for 3 days. He quotes no immediate failures, but admits less than 5 per cent of late relapses.

*A paper read to the Medical Society for the Study of Venereal Diseases, 29th April, 1944.
Laird\textsuperscript{1} in April 1942 using various schemes of dosage—4 grammes for 6 days and 6 grammes daily for 4 or 3 days with and without accompanying irrigations—in 764 cases obtained very similar results in each series with a success varying from 81 to 91 per cent.

Time and extended experience now permit a detached and considered assessment to be made, based on the treatment of some thousands of cases at the Royal Victoria Hospital, Netley, during the last four years.

In 1941 two of us (King and Williams) read a paper to this Society in which we described the results obtained in the treatment of 397 cases of gonorrhoea with a 3-day intensive course of sulphapyridine along the lines first suggested by Bowie, Anderson, Dawson and MacKay. These were compared with a similar number treated for 14 days with non-intensive dosage of the same drug. The results obtained in the two series are here compared with others treated in succession with different drugs and dosage and differing periods of administration. Clearly the possible combinations of these three factors are very large indeed and no one investigation could even begin to cover the ground involved. Nevertheless it is considered that strict comparison of the proportionate results obtained from the considerable number of cases treated does give information which is of value in assessing the drug, the dosage and the duration of treatment which may be expected to produce the maximum number of successes in the minimum time with the minimum number of toxic effects. The aim of this paper is to base the assessment on facts and figures to the strict exclusion of evidence obtained from impressions. In treating a disease so varied in its course and outcome as gonorrhoea, impressions are apt to be particularly misleading, and if these impressions are based on a small number of cases they are often quite erroneous. For instance, when using intensive treatment with sulphapyridine the impression was formed by us that this method was unquestionably superior to other schemes of dosage. In retrospect it seemed that the impression was determined by the clear-cut response to treatment which occurred in the successful cases and by the fact that the proportion of outright successes in the first 100 cases of the group was considerably higher than it was in those subsequently treated. The ultimate assessment showed that in the proportion of immediate successes there was little to choose between those intensively and those non-intensively treated.

In the results which follow it will be noted that our original method when sulphapyridine was being used was to adopt a standard daily non-intensive dosage and to treat for progressively shorter periods in successive groups of cases until the point was reached at which the results began to be unsatisfactory and treatment was clearly inadequate. Thereupon an attempt was made to improve results by increase of daily dosage in the quest for the course of treatment which was shortest and at the same time most effective. The introduction of less toxic and more effective drugs provided a more satisfactory answer to the problem than did sulphapyridine.

This was also the experience of Jefferiss and McElligott who in January 1943 reported the results of their use of sulphasothiazole in 567 cases. They quoted various courses of treatment lasting for 2 days or more. Ninety per cent of 219 cases treated with a dosage either of 6 grammes for 3 days or of 8 grammes for 1 day followed by 6 grammes for 2 days reacted successfully. A further 143 cases were treated by the administration of 6 grammes for 2 days or of 8 grammes for 1 day followed by 6 grammes for a second day; of these cases 89-5 per cent responded successfully. Late relapses are included in these figures. Less satisfactory results (82-2 per cent) were obtained with courses lasting for 12 hours or less.

The 3-day course which is our present routine has considerable advantages. It is effective and it decreases the period of in-patient treatment of Service patients. The toxic effects are very few and the danger of sensitization of patients to sulphonamide drugs is reduced to a minimum. Clearly the next stage of the investigation should be to maintain the present daily dosage and progressively to extend the number of days of treatment to ascertain whether the proportion of successes can be increased by prolonging treatment. Time and material have not yet
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permitted this elaboration, but it is hoped that it will be possible in due course. Once again it is important to emphasize that such a problem cannot be solved by the misleading evidence of impressions. Only the careful study of figures and hard facts will supply the necessary answers.

Details of treatment
All the patients investigated were admitted to hospital and were therefore under strict supervision. In general they were uncomplicated cases of gonorrhoeal urethritis, were not confined to bed and were employed on light ward duties. Tablets were given in 3 equal doses throughout the day; and the doses spaced as far apart as possible. In most of the cases treated with sulphapyridine the toxic effects were found to be diminished when the tablets were given after each of the three main meals of the day. With the less toxic drugs—sulphathiazole and sulphanadiazine—this was found to be unnecessary and tablets were given at 6.30 a.m., 2.30 p.m. and 10.30 p.m. Administration was continued throughout the night in the original intensive series, but this procedure seemed to be of no particular therapeutic advantage and was not adopted in the other series. The tablets were crushed and given in water. The patients were given a full ordinary diet and were encouraged to drink as much fluid as possible—8 pints a day or more if this could be taken. Each patient was seen and examined daily; the tests included a daily microscopical examination of an early morning urethral smear and inspection of the first morning specimen of urine. In most cases a No. 9 pill—calomel grains 2, compound rhubarb pill grains 2, compound colocynth pill grains 2—was given at the beginning of treatment and afterwards when there was any complaint of constipation. Neither urethral irrigations nor local treatments were given during the period when tablets were being taken. If clinical cure was not complete after the first course of tablets, anterior and posterior urethral irrigations with a solution of potassium permanganate 1 in 10,000 were given twice daily and were continued either until evidence of infection had subsided or for one week, after which a second course of sulphonamide tablets was given if necessary, preceded by a leucocyte count as a matter of routine. In the event of failure of the first course of treatment or doubt as to latency of infection it has been customary with us to submit the patient to protein shock therapy in the form of intravenous injection of T.A.B. vaccine by the divided dose method. Twenty-five millions of the mixed organisms are injected intravenously and a similar dose is injected 4 hours later. The result has been a sharp febrile reaction, usually of 102°—104° F. without undue toxic effects (Nicol).

Tests for cure
In the successful case the patient was discharged from hospital after five days' observation without treatment, with absence of morning urethral discharge and absence of haziness or pus threads in the first morning specimen of urine. For the first three weeks after discharge from hospital the taking of alcohol was forbidden and the patient remained under observation by his unit medical officer, whose responsibility it was to examine once in each of the three weeks the first morning specimen of urine for evidence of infection. The patient was then permitted to take alcohol and at the end of three months was readmitted to hospital overnight for examination of an early morning smear and inspection of the all-night urine. The following tests were then performed.

1) Digital rectal examination, 2) microscopical examination of the prostatic secretion, (3) naked eye examination of the urine after prostatic massage, (4) urethroscopy, and (5) Kahn precipitation test for syphilis. If these tests were satisfactory the patient was passed as cured.

Immediate results of treatment
For the purpose of assessing the effectiveness of each scheme of treatment in the production of clinical cure, each series has been divided into three groups (see Table 1) as follows.
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Group A Patients requiring no further treatment after the initial course of sulphonamide.

Group B Patients requiring a small amount of local treatment without further sulphonamide or one intravenous injection of T.A.B. vaccine within 7 days from the end of the course of sulphonamide.

Group C Patients requiring a further course of sulphonamide, irrigations for more than 7 days, further T.A.B. vaccine or hyperthermy.

Groups A and B together include the cases in which success may be attributed to the initial course of sulphonamide. Group C includes all the failures, whether the gonococcus was found in the urethral smear or not.

TABLE 1.—IMMEDIATE RESULTS OF TREATMENT
Complications of the disease and of treatment

<table>
<thead>
<tr>
<th>Grammes</th>
<th>SULPHA PYRIDINE</th>
<th>Sulpha diazine</th>
<th>Sulphathiazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 1/2 x 3</td>
<td>23 in 72 hrs.</td>
<td>4 1/2 x 10</td>
<td>4 1/2 x 7</td>
</tr>
<tr>
<td>No. of cases</td>
<td>397</td>
<td>397</td>
<td>500</td>
</tr>
<tr>
<td>Group A Percentage</td>
<td>198</td>
<td>195</td>
<td>241</td>
</tr>
<tr>
<td>Group B Percentage</td>
<td>50</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>Group A + B Percentage</td>
<td>62</td>
<td>60</td>
<td>86</td>
</tr>
<tr>
<td>Group C Percentage</td>
<td>126</td>
<td>255</td>
<td>327</td>
</tr>
<tr>
<td>Group C Percentage</td>
<td>66</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>Fast cases in Group C Percentage</td>
<td>137</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>Arthritis</td>
<td>——</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Peri-urethral abscess</td>
<td>1</td>
<td>——</td>
<td>——</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>——</td>
<td>——</td>
<td>——</td>
</tr>
<tr>
<td>Haematuria</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Intolerance</td>
<td>80</td>
<td>2</td>
<td>90</td>
</tr>
</tbody>
</table>

Sulphamerazine.—Fifty cases of acute uncomplicated gonorrhoea have been treated with sulphamerazine, 3 grammes daily for 3 days. The makers claim that it is possible to attain with this drug a blood level equivalent to that attained by twice the dosage of sulphathiazole. (It is not considered that the blood level is necessarily a criterion of the therapeutic value of a sulphonamide compound.) Forty-six per cent of these cases fell into Group C, including 32 per cent which were "gonococcus-fast".

Ultimate results of treatment

The difficulties of follow-up of patients from an Army hospital for venereal diseases are obvious. Every effort has been made to obtain details of the later histories of patients but with only partial success. In our early series (see Table 2) follow-up was so incomplete that no adequate figures can be given; the figures in Series 2, Table 1—the intensive group—are taken from our previous paper (King and Williams). Our figures in the groups recently treated with sulphadiazine and sulphathiazole are not yet complete. Cases which relapse after discharge from hospital are the most easily traced and it is probable that a high proportion of these are included in the results. The figures for those which relapse and show positive urethral smears are as follows.

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Series 2  2.5 per cent of 37.5 per cent traced
Series 4  4.3 per cent of 76 per cent traced
Series 5  3.9 per cent of 74 per cent traced
Series 6  3.7 per cent of 70 per cent traced
Series 7  6.2 per cent of 69 per cent traced
Series 8  5.6 per cent of 82 per cent traced
Series 9  3.1 per cent of 51 per cent traced
Sulphathiazole 3.1 per cent of 40 per cent traced

Complications of the disease which occurred after initiation of treatment
Complications of the disease were rare and, as there was no significant difference of incidence in any of the series considered, only the total incidence in all the cases is given. Incidence in individual groups is shown in Table 1. There were 16 cases of arthritis, fasciitis or teno-synovitis, 10 of epididymitis, 5 of acute or sub-acute prostatitis or prostatic abscess and one case of peri-urethral abscess. One only of the cases of arthritis was "gonococcus-fast".

Complications of treatment
The incidence of intolerance or sensitivity to sulphapyridine manifested by the development of rashes or of pyrexia, fell sharply when the length of the course of treatment was reduced to less than 7 days. This incidence in the 14-day course was 20 per cent, in the 10-day course 18 per cent and in the 7-day course 10 per cent, whereas in the 5-day course it fell to 1.3 per cent and did not rise above 0.5 per cent in the others, including the intensive course. There were no cases of agranulocytosis. The usual minor toxic effects of sulphapyridine occurred in every series; vomiting was the most troublesome, but it was rarely sufficiently persistent to warrant withholding the drug. In the series treated with sulphadiazine and sulphathiazole no toxic effects of the drugs were seen except occasional vomiting and headaches.

It may be of interest to mention here in passing the possibility of the desensitization of patients who are intolerant to a sulphonamide. Our experience of this is as yet very slight. We have given sulphathiazole to a few patients sensitive to that drug in gradually increasing amounts; we started with 0.01 gramme and doubled the dose each day until a full daily dose could be tolerated without any ill effect. These were recent cases not included in those under review.

| TABLE 2.—ULTIMATE RESULTS OF TREATMENT |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                  | SERIES 2          | SERIES 4          | SERIES 5          | SERIES 6          | SERIES 7          | SERIES 8          | SERIES 9          | SULPHATHIAZOLE     |
| Groups           | A B C             | A B C             | A B C             | A B C             | A B C             | A B C             | A B C             | A B C             |
| Tests of cure    | 78 19 30 165 93 129 163 115 87 127 109 120 32 100 98 36 106 160 19 18 17 111 35 31 |
| Relapse G +      | 2.5% 3% 3.9% 3.7% 6.2% 5.6% 3.1% 3.1% |
| Relapse non-specific | 8 0 3 5 4 1 7 4 3 7 2 11 0 2 1 2 1 7 1 5 0 9 6 6 |
| Untraced         | 62.5% 24% 26% 30% 31% 18% 49% 60% |
| Totals by groups | 195 60 142 232 134 188 242 163 115 194 173 198 46 151 175 54 189 294 45 46 36 302 119 124 |
| Total cases      | 397 554 540 565 372 537 127 546 |

Haematuria.—Our early lack of knowledge of this subject and its pathology was described in our former paper (King and Williams) in which an account was
given of our experience with 9 cases of renal intolerance to sulphapyridine out of 500 patients treated intensively for gonorrhoea and for non-specific urethritis. Certain recommendations were made at that time which now require modification in the light of our own experiences and those of other workers. When the next 3 cases of haematuria occurred no further action was taken other than the forcing of fluids by mouth. One of the 3 patients caused anxiety in that he did not pass urine until, quite literally, the end of the eleventh hour. In the next 6 cases of haematuria 1,000 cubic centimetres of glucose-saline were given intravenously immediately there was haematuria or lumbar pain in association with the typical acetyl crystals in the urine. Morphine was given when indicated in order to relieve pain. Prompt improvement in every case, with ultimate recovery due to the increased urinary output, was the result.

We feel strongly that masterly inactivity or the administration of fluids by mouth only, in cases of haematuria or of lumbar pain, are policies of danger, and that 1,000 cubic centimetres of fluid intravenously must be given immediately the diagnosis is made. It is equally dangerous to give intravenous injections to patients who are seen when anuria is already present. Anuria of 12 hours’ duration, as Laird has pointed out, requires catheterization and lavage of the ureters.

It is an interesting fact that most patients in whom this complication develops are cured of gonorrhoea with little or no further treatment despite the low total dosage of sulphapyridine. Of the 9 cases which have occurred since our previous paper, 5 patients required no further treatment and the remainder were cured after irrigations had been given for a few days. One of these relapsed but gonococci were not found in the urethral smear; inadvertently this patient was given 4½ grammes of sulphapyridine on each of 2 days. On the third day he had severe lumbar pain and crystals of acetyl sulphapyridine were found in his urine. No cases of haematuria due to sulphathiazole or sulphadiazine have occurred in this series.

In a recent case of non-specific urethritis, however, when the patient was treated with sulphathiazole, pain in the right lower abdomen and fever developed; acute appendicitis was suspected. No microscopic blood was found in the urine and crystals did not appear until twenty-four hours had elapsed. This illustrates two important diagnostic points, first that a moderate fever is not uncommonly present in these cases—it was present in three of our other patients—and secondly that the presenting symptom may be pain over either ureter without lumbar pain.

Failures of treatment

Cases in Group C fall into two main classes: (1) those patients in whom the gonococcus was found in the urethral smear after a first course of sulphonamide had been given, and (2) those in whom urethral discharge persisted but no gonococcus was seen, and in whom evidence of infection in the urine continued. In cases in which the gonococcus was found after the first course and disappeared after a second course of a sulphonamide drug, it was discovered that the organisms will reappear in the urethral smear in a high proportion of cases within a few days after a provocative injection of T.A.B. vaccine given according to the routine described. Both to these patients and to those in whom the gonococcus has persisted throughout, treatment by mechanically induced fever was usually given. The fact that this treatment was available to us influenced our procedure for treatment of resistant cases.

Our findings in the group of patients treated with sulphathiazole show that, if the gonococcus is seen in the urethral smear after the initial course, the chances of cure with a second similar course of sulphathiazole are very much less than in other patients who need a further course of the drug. Forty-one "fast" cases were given a second course of sulphathiazole; only 15 of these patients were apparently cured, 6 went on to pass tests of cure, one relapsed with a positive smear and 8 have not been followed up. In the other group of 59 cases 57 patients were apparently cured by a second course of sulphathiazole; 3 of these relapsed—2 with positive smears—10 passed tests of cure and 44 have not been successfully
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followed up. That is to say, there was only an 8 per cent failure to cure with a second course of sulphathiazole in the post-gonococcal group, compared with a 66 per cent failure in the "fast" cases. Taking the groups in order of time, the incidence of "fast" cases was as follows.

<table>
<thead>
<tr>
<th>Course</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-day</td>
<td>6.3%</td>
</tr>
<tr>
<td>Intensive 3-day</td>
<td>3.5%</td>
</tr>
<tr>
<td>10-day</td>
<td>4.8%</td>
</tr>
<tr>
<td>7-day</td>
<td>5.6%</td>
</tr>
<tr>
<td>5-day</td>
<td>6.7%</td>
</tr>
<tr>
<td>4-day</td>
<td>8.3%</td>
</tr>
<tr>
<td>3-day</td>
<td>10.9%</td>
</tr>
<tr>
<td>3 days (6-41-44)</td>
<td>12.2%</td>
</tr>
<tr>
<td>3 days (6-6-6)</td>
<td>13.1%</td>
</tr>
<tr>
<td>Sulphadiazine</td>
<td>9.5%</td>
</tr>
<tr>
<td>Sulphathiazole</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

Summary and discussion

The drug.—Sulphathiazole and sulphadiazine have appreciable advantages over sulphapyridine in similar doses in the proportion of immediate successes; nevertheless the difference is not as great as many observers have claimed. Both sulphathiazole and sulphadiazine in our hands have shown remarkably few toxic effects and in this respect have great advantages over sulphapyridine. Experience with sulphadiazine however was relatively small. The persistence or reappearance of gonococci in urethral discharges has shown a higher incidence in successive series of cases treated with sulphapyridine over a period of years. There are two possible explanations, first that our non-intensive courses of treatment have become successively shorter and second that either some strains of the organism have become "sulphonamide-resistant" or the number of patients who are unable effectively to use sulphonamide in the tissues is increasing. The latter view has recently been discussed by Harkness and others and need not be considered here. Comparable doses of sulphathiazole and sulphadiazine produced a smaller percentage of "gonococcus-fast" cases than did sulphapyridine. In a small group of cases treated with sulphamerazine according to the dosage recommended by the makers the results were unsatisfactory. The dosage recommended was less than that commonly employed with other sulphonamides.

The dose.—Intensive dosage of sulphapyridine had no advantage over non-intensive dosage except that the percentage of "gonococcus-fast" cases was considerably less. With sulphapyridine the use of a daily dosage of 6 grammes for 3 days gave better results than did a daily dosage of 41/2 grammes for 3 days, and without increase in toxic effects.

The time.—There is no therapeutic advantage in prolonging treatment beyond 5 days and prolongation means an increased incidence of toxic effects. To shorten the course of treatment to less than 5 days diminishes the proportion of successes; there is a distinct fall with a 3-day dosage. This may be counterbalanced by an increase in the daily dosage. In general the shorter the non-intensive course the higher the proportion of "gonococcus-fast" cases.

Conclusions

(1) Sulphathiazole and sulphadiazine are the drugs of choice in the treatment of acute gonorrhoea. Sulphadiazine has no advantage over sulphathiazole in our small experience of the former drug.

(2) Intensive dosage is no better than non-intensive dosage, except that a high initial dose appears to decrease the number of "gonococcus-fast" cases.

(3) There is no indication for the prolongation of treatment for more than 4 or 5 days.

(4) The success of a 3-day course of sulphapyridine is dependent upon an increase of daily dosage from 41/2 grammes to 6 grammes. A similar dosage of 6 grammes for 3 days of sulphathiazole or of sulphadiazine gives good results.

(5) The clinical picture of renal intolerance to sulphapyridine is not always clear cut. Successful treatment of the condition requires early diagnosis and the immediate intravenous infusion of saline. The intravenous administration of salines is contra-indicated when anuria has developed.

(6) The incidence of "gonococcus-fast" cases has increased as the non-intensive courses have been shortened. This may however be due, with the passage of time, either to a real
increase in "drug fastness" on the part of the organism or to drug tolerance on the part of the host. Our intensive course of 1940 gave the lowest proportion of "fast" cases— 

a proportion which is considerably lower than that in those groups treated with sulphathiazole and sulphanilamide within the last year.

(7) Sixty-six per cent of "gonococcus-fast" cases were not cured by a second course of sulphathiazole (6 grammes daily for 3 days after an interval of one week) whereas 92 per cent of non-gonococcal cases were so cured.

(8) The figures presented show a lower proportion of successes than those recorded by most observers. This may be due to the fact that both "gonococcus-fast" cases and those with evidence of persistent infection in all-night urines, but without gonococci in urethral smears, are counted as failures.

Our acknowledgments are due to Brig. T. E. Osmond, A.M.S., for helpful encouragement, and to Col. G. P. Kidd, M.C., A.M.S., for permission to publish details of these cases.

REFERENCES

— (1942) ibid., 2, 527.

DISCUSSION

Brig. T. E. Osmond, the President, said that they had all listened with great interest to the cases recorded by Maj. Williams. The numbers were so considerable that the results were both impressive and valuable; it was probably the largest series yet recorded in Great Britain. The speaker was much interested in what Maj. Williams had said about the intravenous injection of anti-typhoid-paratyphoid vaccine. It was the speaker's experience that it was bordering on the dangerous, but they appeared to have had little trouble at Netley—probably because of the skill with which the procedure was used.

The speaker agreed with what had been said about the length of the course. He had always been of the opinion that a week was the maximum period over which large doses of sulphonamides should be given; preferably the period should be rather less. In most cases from four to five days was the best.

The question of the cause of sulphonamide-fastness was a matter of very considerable speculation, but it seemed to him that if the use of sulphonamides were continued in the treatment of gonorrhoea, as time went on there would be more and more resistant strains of the organism, owing partly to the fact that strains acquired resistance, and partly to the fact that sensitive strains would be killed off. An increase in the fast cases would be most embarrassing until penicillin became available as a solution of most of the difficulties. Even then there might prove to be penicillin-fast cases.

Lt.-col. D. J. Campbell said that the experience he wished to describe was more recent than that covered by the figures quoted by Maj. Williams. In one of the first discussions on the subject the speaker had strongly advocated a 5-day course and for a long time had found that course best whichever drug was used. On the introduction of the 2-day sulphathiazole course of 5 grammes a day and in consideration of the great success claimed for it, he had changed over to it, but even under the best conditions had never obtained more than 71 or 72 per cent of proved cures. Similarly with sulphanilamide, when 6 grammes a day for 3 days had been given the results were almost the same as had been those when 10 grammes of sulphathiazole had been administered in 2 days.

During the last nine months he had been in the Mediterranean theatre of war. Experience of the use of sulphonamides there had been dramatic. In North Africa, when sulphathiazole was available, the 2-day course of 5 grammes a day was given in all cases of acute gonorrhoea. On the whole his experience in North Africa had been very similar to the experience of workers at home. Such failures as there had been, very often had been attributable to the heat, to the difficulty of therapy during action and to the considerable lack of fluid intake on account of water shortage; under the best conditions response had been comparable with that at home.

The result was that the authorities had not been led to regard venereal disease as a very serious problem from the treatment standpoint. In Sicily and in Italy, however, from the very first catastrophe had overtaken them. Whereas some 65 or 70 per cent of patients had recovered completely on whatever initial course of sulphanpyridine or sulphathiazole had been given, the