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II

INTENSIVE TREATMENT OF GONORRHOEA AND NON-SPECIFIC URETHRITIS WITH SULPHAPYRIDINE * †

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THE effectiveness of sulphapyridine in the treatment of gonorrhœa has never been seriously questioned. From the first results were universally good and led naturally to a spirit of extreme optimism which has now given place to the realisation that there are problems still to be solved, not the least of which is the difficult problem of dosage. From the many and varied schemes of treatment which are used it is clear that there is no general agreement as to the routine dosage which will produce the highest proportion of good results while yet avoiding undue toxic effects. Most workers in the subject now stress the importance of a high constant level of blood sulphapyridine maintained by giving larger doses at first followed by smaller doses at short intervals ; and certainly the general experience is that to give small doses at first is to risk disaster in the form of the resistant or "sulphonamide-fast" case. Bowie, Anderson, Dawson and Mackay (1939) were the first to record their experi-

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ences with massive initial dosage followed by rather large doses over a short period. In the course of review of experience with various schemes of dosage they described the effects on 23 men with gonorrhœa of the following treatment :

4 grams of sulphapyridine at once ; 2 grams of sulphapyridine after four hours, then 1 gram every four hours during the waking periods, the total dosage spread over seventy-two hours, making a total of from 15 to 20 grams. This has been called the " 8—4—2 " treatment, from the number of tablets administered at successive intervals, and also the " Aberdeen method." Treatment given by this or similar schemes will be referred to in this paper as " Intensive Treatment." Of the 23 patients in this series twenty were cured without further treatment and one was probably so cured. In this group there was a high incidence of unpleasant although not serious toxic reactions and, although these patients were actually treated as out-patients, the desirability of strict control of such treatment under in-patient conditions is clear. This probably accounts for the fact that there are few records in the literature of the use of this treatment. It was to be anticipated that a method which, under conditions of strict observation and control, promised to give rapid and efficient results would be of considerable interest to the fighting services and, in fact, the other two publications which we have traced came from this source. Buist and Simon (1940) treated 20 men suffering from fresh uncomplicated gonorrhœa according to the scheme of dosage outlined above. All responded to the treatment and the average length of stay in hospital was 5·3 days. During periods of observation and tests varying from two to three months one relapse occurred.

Petro (1940) treated 100 patients, 27 of them with a course almost identical with that first used by the Aberdeen school, in which the period of treatment was seventy-two hours and the tablets were given during the day only, the total sulphapyridine in each case amounting to 16 grams. The remaining 73 received a preliminary dose of vaccine consisting of twenty million gonococci given intradermally, followed by a course of sulphapyridine consisting of 4, 2, 1 grams at intervals of four hours and then one gram four-hourly day and night for a total of forty-four hours. The amount of sulphapyridine

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administered in each case was again 16 grams. In the first group the average time taken to achieve clinical cure was 9.07 days. Three failed to respond but, in a follow up period of two months, there were no relapses in the successful cases. In the second group the average time before clinical cure was 6.7 days; two failed to respond and there was one relapse after apparent success. Toxic manifestations were of a minor character except in two cases, in one of which hæmaturia occurred and in the other renal colic with microscopic evidence of blood and crystals in the urine. In both cases the symptoms subsided promptly when the drug was discontinued. Failures were attributed to faulty drainage resulting from narrow external urinary meatus, from "pocketing" of infection in Littre's glands or from urethral stricture due to past infection.

DESCRIPTION OF CLINICAL MATERIAL

In our series the total number of patients treated intensively was 502 including 397 whose urethral smears showed gonococci and 98 in whom the gonococcus was not found. Seven were suffering from infections such as cystitis which are not relevant to the present investigation.

Of the 397 patients with gonorrhœa 16 had had recent gonorrhœa treated with sulphonamide preparations and were presumed to have relapsed. Thirty-nine others gave the history of an attack of gonorrhœa in previous years. Five had received small doses of sulphonamide preparations before admission to hospital; but the dosage given was insufficient to produce any beneficial effect and all continued to show gonococci in smears.

Of the 98 patients diagnosed as suffering from non-specific urethritis 20 admitted to a previous attack of gonorrhœa and 10 to previous attacks of non-specific urethritis. One had had inadequate treatment with sulphonamide before admission. Most of the men in this group admitted having taken a risk of infection.

Almost all these patients reported sick at once when symptoms appeared and were immediately admitted to hospital for treatment. Of 397 men with gonorrhœa only 31 had had symptoms for more than one week. Of 98 men with non-specific urethritis 14 had had symptoms

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for more than a week. The remainder in each category had noticed symptoms for periods varying from a few hours to seven days, but in the large majority treatment was instituted within the first three days.

Under these circumstances the number of patients with complications before treatment was started was small, as might be expected.

Among the patients with gonorrhoea there were: 6 cases of epididymitis; 1 infection of Tyson's gland; 1 infection of a para-urethral duct.

Among the patients with non-specific urethritis there were: 5 cases of epididymitis; 1 case of fibrositis.

DETAILS OF TREATMENT

The broad outlines of our scheme of treatment remained unchanged throughout the four months in which we used this intensive course; but as our experience of the toxic effects of the drug grew a number of modifications were made. From the first all patients were kept strictly in bed during the seventy-two hours in which they were taking sulphapyridine, on a "milk diet" consisting of two to three pints of milk daily with rice, bread and butter or margarine. Temperature was taken morning and evening. In 402 cases an initial dose of 8 tablets of sulphapyridine was followed by 4 tablets in four hours' time and thereafter by 2 tablets every four hours day and night to the seventy-second hour when the last dose was given—a total of 23 grams. 100 patients were treated by an 8—6—4—2 tablets scheme, a total of 25 grams. In all cases the actual taking of tablets was supervised so that doses could not be missed. In most cases the tablets were swallowed whole and a large drink of water given immediately afterwards. It was soon evident that as far as the patient was concerned the most troublesome effect of the treatment was the high incidence of vomiting. The suggestion was made that constipation might be a predisposing factor and therefore, in all later cases a "No. 9" pill, consisting of calomel grains ii, compound rhubarb pill grains ii, compound colocynth pill grains ii, was given at the beginning of the treatment. It seemed that the incidence of vomiting was slightly less in consequence. At first the possibility of severe damage to the bone marrow was feared and daily white cell counts were

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done. Later the cell count on the second day was given up, and finally a count was done on the third morning of treatment only unless there was some special indication at another time. Early morning smears and urine were examined daily during treatment. No urethral irrigations or other local treatments were given.

The incidence of certain renal complications—to be discussed later—brought in its train further additions to the routine. The daily fluid intake and output were measured, alkali was given by mouth, at first in the form of sodium bicarbonate, 1 drachm to the pint of water, in as large quantities as the patients could be persuaded to take (Long and Bliss, 1939)—and later as potassium or sodium citrate grains xxx two-hourly throughout the twenty-four hours, since sodium bicarbonate of itself seemed to encourage vomiting in some cases and was so unpalatable that difficulty was experienced in ensuring that it was taken in adequate quantities. Patients were of course examined daily and carefully questioned as to abdominal symptoms, particularly pain. The urine was watched for macroscopic and, in certain cases, for microscopic evidence of blood.

PROCEDURE FOR OBSERVATION AND TESTS OF CURE

At the end of the three-day course of treatment patients were allowed up and were usually fit to perform light ward duties. After treatment close observation under in-patient conditions extended over a period of at least seven days and longer if there was doubt about clinical cure. In each case on three or four occasions during this period an attempt was made to obtain and examine a urethral smear before the first morning specimen of urine was passed. At the same time the first morning specimens of urine were examined by naked eye, and the persistent presence of leucocytes in the smear during the period of observation, or of haziness or pus threads in the urine, was accepted as evidence that cure was not complete and that further observation or treatment was required. The repeated naked-eye examination of such all night specimens of urine by the experienced observer, supported by microscopic examination of threads when necessary, is probably the most reliable of all single tests for latency of gonorrhœa. This test is still

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more reliable if alcohol is taken beforehand. If at the end of seven days morning smears and urine were satisfactory the following tests were performed :

- (1) Rectal examination.
- (2) Microscopic examination of a prostatic bead.
- (3) Naked-eye examination of the urine after the prostatic massage.
- (4) Urethroscopy.

These tests were followed by another examination of morning smear and urine on the day after instrumentation. If all the tests were satisfactory the patient was discharged from hospital.

Arrangements were made with the man's unit for him to attend at hospital once a week for three weeks for urethral and prostatic smear and for examination of the urine. Finally, three months after discharge from hospital, each patient was re-admitted and all tests repeated with the addition of a complement fixation test for gonorrhœa on the blood serum. If the tests remained satisfactory the patient was discharged as cured.

The difficulties of maintaining these standards under war-time conditions are obvious. Units are moved from place to place, from Command to Command and overseas. As far as possible these men have been followed through their period of three months' observation but there are large gaps in the information and these will be indicated. It may be argued that three months is too short a time for observation in view of the fact that relapses after treatment with sulphonamides have been described after longer intervals. The force of this criticism must be admitted but it is not possible to provide for every contingency in a disease so variable in its outcome as gonorrhœa and, probably, the standards of observation and testing were as high as could be attained in the circumstances. The question of relapse is in any case a difficult one. No method of hard and fast distinction between relapse and reinfection has yet been devised. Histories are misleading and even the certain knowledge that sexual intercourse has taken place is no sure evidence that reinfection has occurred. It is well known that intercourse is one of the common factors which may convert latent into declared infection.

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IMMEDIATE RESULTS OF TREATMENT

For the purpose of assessing the effectiveness of this scheme of treatment in producing clinical cure each group is divided into three sub-groups according to the amount of treatment ultimately required and in each sub-group the average length of time that these patients were detained in hospital is indicated. This last is in many respects an inaccurate index of the success or failure of this treatment. In using a scheme of dosage with which we were unfamiliar it was a natural tendency to prolong rather than to shorten the period of observation. This also depended to a great extent, as it proved, upon the view of the individual medical officer. The facts that these men were drawn from a large and scattered Command and that units were often situated many miles from the Command treatment centre, had to be taken into consideration and demanded longer observation than would have been necessary in a compact area.

The sub-grouping is as follows :

Gonorrhœa.—The total number of patients was 397.

(1) Patients requiring no further treatment after three days' intensive treatment numbered 195, or 49 per cent. of the total. The period of stay in hospital varied from 11 to 28 days, the average time being 13 days.

(2) Patients requiring a small amount of extra treatment such as one intravenous injection of T.A.B. vaccine or urethral irrigations for a few days only numbered 60, or 15 per cent. of the total. In-patient stay varied from 15 to 38 days and the average was 23 days.

(3) Patients requiring a further course of sulphonamide, irrigations and T.A.B. combined, or other combinations of these treatments numbered 142, or 36 per cent. of the total. Five of these patients in sub-group 3 are still in hospital after treatment for periods of from 83 to 110 days. The remaining 137 were in hospital for an average time of 44 days, the shortest period being 18 days and the longest 114 days.

"Sulphonamide Resistance."—Fourteen patients in this series were suffering from infections which proved "sulphonamide-resistant" in that gonococci were still present in the urethral secretions when the intensive course of treatment was finished and persisted for variable periods from the fourth day up to three months. Bowie and his co-workers state, in their original article

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that, in a few cases, gonococci were present in a mucoid secretion at the end of intensive treatment but disappeared at once, the patient making a prompt and satisfactory recovery. In our series this occurred in only one case, which is included in the first and most satisfactory group, since no further treatment was required and the patient was discharged from hospital after fourteen days. One other made a prompt recovery after an additional intravenous injection of T.A.B. and is included in the second group. The remaining twelve were very resistant and required prolonged treatment. They are included in the third group and one is among the five patients still in hospital.

COMPARISON WITH PATIENTS SUFFERING FROM GONORRHŒA AND TREATED WITH A ROUTINE NON-INTENSIVE COURSE

For the purposes of this comparison the records were taken at random of an identical number of cases, 397, treated with a fourteen-day course of sulphapyridine consisting of 4 grams daily for three days followed by 3 grams daily for eleven days without irrigations. The standards of observation and tests were identical. The following is the result of assessment of these cases under the same headings :

- (1) 198 or 50 per cent. required no additional treatment. The length of stay in hospital varied from 12 to 37 days and the average was 30 days.
- (2) 62 or 16 per cent. required a small amount of additional treatment. Stay in hospital varied from 14 days (in a patient whose course was curtailed through toxic effects), to 29 days. The average length of stay was 20 days.
- (3) 137 or 34 per cent. required considerably more treatment. Stay in hospital varied from 20 to 223 days, with an average of 56 days. Twenty-six of these cases, all included in sub-group 3, proved "sulphonamide fast."

NON-SPECIFIC URETHRITIS TREATED INTENSIVELY

The total number of patients was 98 ; of these two became seriously ill as a result of treatment, one with fatal outcome, and are not included in this assessment.

- (1) 27 or 28 per cent. of the total (96) required no additional treatment. The length of stay in hospital varied from 9 to 23 days and the average was 13 days.

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(2) 7 or 7 per cent. required a small amount of additional treatment. Stay in hospital varied from 18 to 30 days, and the average was 23 days.

(3) 62 or 65 per cent. required considerably more treatment, for 57 of these the stay in hospital varied from 20 to 112 days and the average was 48 days. The other 5 are still in hospital after 75, 83, 100, 105 and 124 days respectively.

COMPARISON WITH PATIENTS SUFFERING FROM NON-SPECIFIC URETHRITIS TREATED WITH ROUTINE NON-INTENSIVE COURSE

The records of 98 patients with non-specific urethritis who had received the routine fourteen-day course without urethral irrigations were taken at random.

(1) 34 or 35 per cent. of the total required no additional treatment. Stay in hospital varied from 15 to 32 days and the average was 21 days.

(2) 6 or 6 per cent. required a small amount of additional treatment. Stay in hospital varied from 20 to 32 days, the average being 26 days.

(3) 58 or 59 per cent. required considerably more treatment. Stay in hospital varied from 32 to 130 days; the average was 60 days.

THE EFFECT OF DURATION OF THE INFECTION UPON THE RESULTS OF TREATMENT

As previously stated the very large majority of these men began treatment during the first week following the onset of symptoms. Those with discharge for more than one week were only 27 in number and fall into the appropriate sub-groups as follows: (1) 14 or 52 per cent.; (2) 2 or 7 per cent.; (3) 11 or 41 per cent.

The average time of stay in hospital for all these cases was 27 days. Obviously conclusions cannot be drawn from this small number of cases but, for what the evidence is worth, there appears to be no difference between this group and the majority.

COMPLICATIONS OF INFECTION ARISING DURING TREATMENT

Gonorrhœa Treated Intensively.—The following complications occurred: 1 case of epididymitis supervened on the third day, 1 case of arthritis of knee on the fourth

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day, 1 case of multiple arthritis on the seventh day and 1 case of latent prostatitis was discovered as the result of tests for cure.

Control Cases of Gonorrhœa.—There were 9 cases of soft stricture of the urethra and in one case a fibrous stricture was found at final test five months later in a man with no history of previous gonorrhœa. In addition there was one case of periurethral abscess and one of epididymitis occurring on the eighth day.

Non-Specific Urethritis Treated Intensively.—The following complications occurred: 1 case of subacute prostatitis occurring after $2\frac{1}{2}$ months; 1 case of arthritis of the knee on the tenth day; 1 case of epididymitis in the seventh week; 1 case of multiple arthritis beginning on the fourth day.

Control Cases of Non-Specific Urethritis.—Soft strictures were found subsequently in 5 cases; there was 1 case of epididymitis on the sixth day and also 1 case of metatarsalgia on the eighth day.

ULTIMATE RESULTS OF TREATMENT

The difficulties of carrying this investigation to its ultimate conclusion have been indicated. As regards control patients it has been impossible to obtain figures which would be of any value. Every effort has been made to obtain details of the later history of patients treated with the intensive method. Many are serving overseas and details are not yet available. Others did not start their treatment until the end of December and early January and, at the time of writing, are not yet due for their final tests. Of the patients with gonorrhœa 127 are known to have passed all their tests satisfactorily—78 from group (1), 19 from group (2), and 30 from group (3).

Of the patients with non-specific urethritis there are records of 16, 9 in group (1), one in group (2), and 6 in group (3), who have passed all tests.

Relapses.—From the group of patients with gonorrhœa 21 are known to have relapsed. Of these 15 were in group (1), 7 of these having positive smears; 1 in group (2), having a positive smear; 5 were in group (3), 2 of these having a positive smear.

From the cases with non-specific urethritis, 1 from group (1) is known to have relapsed and 2 from group (3).

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These results are still coming in and the ultimate assessment will include a considerable proportion of the total number treated.

THE COMPLICATIONS OF TREATMENT

Minor Toxic Effects.—Most of the complications were of a minor character although unpleasant and often distressing to the patient. These occurred in the following order of frequency: vomiting, headache, nausea and feeling of distension, anorexia, persistent low backache, insomnia, depression, leucopenia, skin rashes. Vomiting was the only symptom of this character which assumed important proportions. It occurred in more than 60 per cent. and in half of these it was severe enough to cause considerable distress and to handicap treatment. Nevertheless, in no case was treatment stopped on account of it. The administration of alkalis in the form of sodium bicarbonate, 1 drachm to the pint of water, or of potassium or sodium citrate grains xxx two-hourly, seemed to control vomiting to some small extent. All patients were free from these minor complaints within twenty-four hours of the termination of the treatment.

White cell counts did not fall below 5,000 per c.mm. in any case; but in one instance in which the total count was 5,200 per c.mm. the percentage of polymorphonuclear leucocytes fell to 43 and it was thought advisable to stop treatment after 18 grams of sulphapyridine had been taken.

Rashes occurred in only three patients. One developed an urticarial rash with swelling of the eyelids, on the third day of treatment. The other two developed rashes of the morbilliform type on the fifth and sixth days after the start of treatment respectively.

Major Toxic Effects.—The complications in this group were all of renal origin. Cases of renal intolerance to sulphapyridine are relatively uncommon but the subject is one which has accumulated a considerable literature. No less than 45 articles on this subject were found. The general experience seems to have been remarkably uniform and corresponds closely with our own. The manifestations of intolerance tend to occur early, usually on or about the second or third day of treatment, and are of sudden onset. They have been described with both intensive and non-intensive dosage but seem to be more

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common with the former. Hæmaturia is the most constant and in many cases the first symptom of renal damage. Other symptoms are severe lumbar pain, often unilateral at first, which may require morphia for its relief, true renal colic, oliguria and anuria which, in some cases, in spite of treatment goes on to uræmia. Vomiting is usually persistent and severe. In several of our cases there was a marked abdominal distension, a symptom to which there appears to be no reference in the literature. In all cases sheaves of jagged crystals consisting of the acetyl derivative of sulphapyridine were found in the urine. There are records of ten fatalities and post-mortem investigation of some of these showed blockage of the vesical ends of both ureters with concretions formed of this crystalline deposit of acetylated sulphapyridine.

In our series of 502 patients treated intensively there were 5 cases of anuria. Two of these developed uræmia and one died in consequence. A description of both these cases will be given including details of post-mortem examination of the patient who died, which gave evidence of blockage of the vesical ends of both ureters although no actual concretions were found. All these patients had hæmaturia and lumbar pain. Two other cases of hæmaturia and two of severe lumbar pain occurred but anuria did not supervene. It is possibly significant that four cases of anuria, including the two in which uræmia developed, one of hæmaturia and one of lumbar pain occurred in patients receiving the 8, 6, 4, 2 (tablets) dosage as opposed to the routine 8, 4, 2 dosage which the others were given. The records of over 2,000 patients treated by non-intensive therapy with sulphapyridine during the past year show that there have been two cases of anuria and three of hæmaturia. The two patients who suppressed were receiving three grams of the drug daily when the complication occurred.

The causes of this serious and potentially dangerous complication are not fully understood, but there is evidence to suggest (Baines and Wien, 1939) that, whereas many if not all patients excrete up to 50 per cent. of their sulphapyridine in the acetylated form, in only few patients does massive precipitation occur in the course of excretion. This may be due to idiosyncrasy but it seems clear that diminution of fluid excretion with

consequent increased tubular concentration of sulphapyridine or its acetyl derivative, and perhaps acidity of the urine, increase the likelihood of deposition of crystals. It is interesting to note that renal complications, which developed in six patients receiving the 8, 6, 4, 2 dosage, occurred in rapid succession in a group of patients who were in the same ward at the same time. Previously 90 men had been treated similarly without mishap. Investigation of the circumstances showed that these men objected to, and either evaded or surreptitiously disposed of the sodium bicarbonate solution which they were ordered to drink. In the light of experience gained it seems probable that too much faith was placed in the administration of alkali with failure to make certain that sufficient fluid was taken. The bicarbonate solution was unpalatable and these men were convinced that it made them vomit. In neglecting to take the bicarbonate solution they also failed to take sufficient fluids. Afterwards this difficulty was adjusted satisfactorily by giving palatable fluids, such as barley water and lemonade in large quantities, and by giving alkali in small bulk in the form of sodium citrate solution grains xxx to the dose two-hourly.

The following precautionary measures are recommended for patients undergoing intensive treatment in addition to those mentioned in the details of treatment.

(1) The urine should be tested for albumin before the treatment is begun.

(2) Large quantities of fluid should be given by mouth in palatable form.

(3) Some of these men are not used to taking large quantities of fluid and constant supervision is essential to see that they do so.

(4) Alkali should be given in the form of potassium or sodium citrate grains xxx two-hourly. The value of alkali in preventing renal complications has been questioned and is uncertain. It was decided to continue giving it until further evidence was obtained as to its efficacy; but certainly it is of less importance than the forcing of fluids. The reaction of the urine should be tested each morning, acidity of the urine being an indication for more energetic use of alkalis. In most of our patients the reaction of the morning urine was neutral.

(5) The total quantity of urine passed each day by

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each patient should be measured. Diminution of the amount in a patient known to be taking and retaining large quantities of fluids would be an indication to stop treatment.

(6) In cases of persistent vomiting fluids should be given by the intravenous drip method if the treatment is to continue.

(7) The following are indications for stopping the drug: (a) Hæmaturia. (b) Severe lumbar pain. (c) Intractable vomiting. (d) Diminished excretion of fluids.

(8) If anuria supervenes operative treatment as outlined below should not be delayed for more than 12 to 24 hours.

The following is a description of the two cases in which uræmia developed: the early stages of their condition resemble closely those found in the other cases of anuria.

Case 1.—Lance-Corporal M., admitted December 9, 1940, with relapsing non-specific urethritis this being the fourth attack since 1938. On examination a thin mucoid urethral discharge showing leucocytes, secondary organisms and epithelial cells was found. He was given intensive treatment (8, 6, 4, 2, 2, 2, 2, 2, 2 tablets), 16 grams in thirty-six hours. After thirty-six hours he developed hæmaturia and pain in the right loin which required morphia for its relief. The urine contained crystals of acetyl sulphapyridine. Tablets were stopped at once, but suppression of urine supervened and continued for some days in spite of treatment. During the night of December 15-16 his condition deteriorated rapidly and marked greyish cyanosis, dyspnoea, with sighing respirations, cough and frothy blood-stained discharge from the nose were present. He was unconscious and had epileptiform convulsions. Face and neck were puffy but there was no actual pitting œdema. There were signs of right heart dilatation and failure with œdema of the lungs and distended veins in the neck. The blood urea rose from 63 mgm. per 100 c.c. on December 12 to 400 mgm. per 100 c.c. on December 16, the systolic blood-pressure was 180 and the total white cell count rose to 21,200 per c.mm. Marked leucocytosis was a feature of all cases in which renal complications occurred. The following treatment was given:

Continuous oxygen by nasal tube; lavage of the lower bowel followed by rectal infusion of 30 per cent. magnesium sulphate solution; venesection with withdrawal of 14 oz. of blood followed after two and a half hours by the removal of another pint of blood and intravenous infusion of 4.286 per cent. sodium sulphate and 10 per cent. glucose in normal saline. That evening (December 16) he began to pass urine and voided 9 pints during the succeeding twelve hours. From this point he made an excellent recovery and on December 21 the blood urea was 35 mgm. per 100 c.c., the patient was normal in appearance and felt well. The urine showed a faint cloud of albumin but there were no pus, red-blood-cells or casts seen in the centrifuged specimen. On December 28 he was discharged from hospital and returned early in February looking and feeling well, the urine showed no abnormality,

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the blood urea was 34 mgm. per 100 c.c. and the urea concentration test showed normal renal function.

Case 2.—Corporal B., admitted on December 18, 1940 with non-specific urethritis. He was given intensive treatment (8, 6, 4, 2, 2, 2, 2, 2, 2, 2 tablets), 17 grams in forty hours, but after forty hours (December 21) he complained of severe colicky pains in the loins and lower abdomen and the drug was discontinued. Morphia was required to relieve the pain. The patient vomited periodically; there was no abdominal distension. The total white cell count of the blood was 12,800 per c.mm. rising later to 17,200 (on December 23). During the twenty-four hours that followed several small specimens of urine, heavily stained with blood, and containing crystals of acetyl sulphapyridine, were passed at intervals. On December 22 the blood urea was 73 mgm. per 100 c.c., rising to 94 on the following day and reaching 300 on the day of death. Treatment was given as outlined in the previous case, but without success. He became drowsy with puffy face, sighing respirations, frequent vomiting and fits. He died on December 27.

The pathological findings in this case form the subject of a separate communication by Major N. T. Whitehead, R.A.M.C., to which reference should be made, but the following is a summary of his report and of his suggestions as to the probable sequence of events.

Death in this case was due to the blocking of both ureters by "altered" blood with subsequent anuria and uræmia.

Sulphapyridine crystals were formed in the tubules and were then either forced through the walls of the tubules into the surrounding interstitial tissue or else passed down the tubules into the renal pelvis and thence into the ureters. Many of those crystals which were side-tracked into the kidney substance damaged adjacent blood capillaries and caused a number of small hæmorrhages. Some of the extravasated blood found its way down the tubules into the ureters. The crystals which reached the renal pelvis continued their journey down into the bladder but in so doing damaged the walls of the ureters causing subepithelial hæmorrhages. This was particularly so at the ureteral orifices whose lumina were much reduced in consequence. The narrowed lumina and the sludge-like "altered" blood were held to account for the blockage of the ureters and the fatal consequences.

In the light of after knowledge it is clear that the correct procedure in these cases was to catheterise the ureters and wash out the kidney pelvis and ureters in an attempt to clear the obstruction. Unfortunately, we had

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little knowledge of this complication and its pathology at this time, and this procedure, which might have saved the second patient, was not carried out.

TOXIC EFFECTS IN THE CONTROL GROUP OF 495 CASES TREATED WITH THE ROUTINE FOURTEEN-DAY COURSE OF SULPHAPYRIDINE

The toxic effects of treatment of this type are now common knowledge, but the details in this group of cases are included for purpose of direct comparison.

Most of these patients suffered to a minor degree from insomnia, anorexia, depression, headache and vague abdominal discomfort. While nausea was the rule, vomiting was unusual and in only three cases was treatment stopped for this reason; in three others who were vomiting, the dose of sulphapyridine had to be reduced. Toxic rashes were the most marked feature occurring in 95 or 19.2 per cent. of the cases; these eruptions were of the morbilliform or scarlatiniform type with, rarely, an urticarial element. They were associated with an increase in the severity of the general toxic reactions, frequently with pyrexia and sometimes with a low grade pharyngitis. In 18 of the cases with rashes treatment with sulphapyridine was stopped; in 55 the course was completed with the same doses of sulphanilamide; in the remaining 22 treatment with sulphapyridine was continued to the end of the course. There was one case of hæmaturia and none of agranulocytosis.

COMMENT

The number of cases is small; the follow-up is incomplete and no figures are available for comparison of the end results obtained with the two schemes of dosage. Under these circumstances, no conclusions can be drawn from this investigation; but certain interesting facts emerge. While treating the patients the impression was formed that the intensive method was decidedly superior to other schemes of treatment which had been used. This impression was probably determined by the prompt and clear-cut response to treatment which occurred in the successful cases, and by the fact that the proportion of immediate, group (I), successes was considerably higher in our first 100 cases than in those treated subsequently. In this first 100, 69 were clinically cured after

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three days of treatment ; and our first " sulphapyridine-fast infection " was not until the 114th case. That this impression was not altogether justified is shown from the figures which run a close parallel in the intensive and non-intensive groups.

The following advantages may be claimed for the intensive method, at any rate as far as the treatment of gonorrhœa is concerned :

(1) The period of stay in hospital is shortened.
 (2) The unpleasant complications of treatment which commonly occur on or about the ninth day, namely pyrexia, malaise and toxic eruptions, are eliminated for practical purposes.

(3) The danger of toxic effects upon the bone marrow is less with a three-day course of treatment than with a full fourteen-day course.

(4) The incidence of " sulphonamide-fastness " and of urethral infiltrations was markedly diminished. In preventing these the addition of urethral irrigations to the routine fourteen-day course would in all probability be equally effective.

(5) The treatment is more economical in that fewer tablets are required and in-patient treatment is curtailed.

Attention is drawn to the following disadvantages :

(1) During the short period of treatment many patients vomited a great deal and felt unwell ; on the other hand in many cases the malaise was no worse than is commonly experienced with routine non-intensive dosage. Those patients who had experience of both were questioned and all stated that they preferred the intensive treatment owing to its short duration.

(2) Renal complications were more common. No doubt the incidence in this series was exceptionally high and it is believed that with the help of present experience it would be possible to avoid the more serious effects of these complications.

(3) The treatment is not practicable under out-patient conditions.

In view of the fact that we were inexperienced with the method and deliberately prolonged observation and in-patient stay in these cases, it may be that the scales of this investigation are to a certain extent weighted against the intensive method, and that, with the help of experience gained, better results could be obtained

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and the period of treatment shortened in those patients who do not immediately respond to the three-day course.

The proportion of immediate successes in patients with gonorrhoea in both intensive and non-intensive groups is less than that which has been claimed in the large majority of publications on the subject, although the totals shown by the combination of groups (1) and (2) are not far short of the percentages of success which are claimed by most workers who have used sulphapyridine without irrigations. We attribute the difference to the routine tests involving the examination of the morning smear and the all-night urine during the period of observation. In previous work in civil clinics it was not possible to apply these tests as a routine and it is believed that some latent infections escaped notice and further treatment in consequence.

SUMMARY

(1) 502 patients, including 397 who were suffering from gonorrhoea and 98 who were suffering from non-specific urethritis, were treated with a three-day course of intensive treatment with sulphapyridine, along the lines first suggested by the Aberdeen school.

(2) Of the patients with gonorrhoea 49 per cent. required no further treatment and remained in hospital an average period of thirteen days; 15 per cent. required a small amount of extra treatment and remained in hospital an average period of twenty-three days, and 36 per cent. required considerably more treatment with an average in-patient stay of forty-four days.

(3) Of the patients with non-specific urethritis 28 per cent. required only the initial course and the average length of stay in hospital was thirteen days; 7 per cent. required slightly more treatment, remaining in hospital an average of twenty-three days, and 65 per cent. had considerably more treatment, the in-patient stay amounting to an average of forty-eight days.

(4) A comparison with the same number of cases treated non-intensively with a fourteen-day course of treatment showed that in the two groups there was little difference in the proportion of successes, although in-patient stay was shortened for patients treated successfully with intensive dosage.

(5) The complications of the treatment consisted of

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minor toxic effects, of which vomiting was the most frequent and troublesome, and of toxic effects on the kidney due to excretion of crystals of the acetyl derivative of sulphapyridine. In consequence there were two cases of hæmaturia, two of severe lumbar pain, and five cases of anuria, in two of which uræmia developed, one terminating fatally. Methods of avoiding or minimising these complications are discussed.

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III

INTENSIVE TREATMENT OF GONORRHŒA AND NON-SPECIFIC URETHRITIS WITH SULPHAPYRIDINE

DISCUSSION

DISCUSSION OF THE PAPER READ BEFORE THE M.S.S.V.D. on 28.3.41
BY LIEUT.-COLONEL A. J. KING AND MAJOR D. I. WILLIAMS

MAJOR T. E. ANDERSON said he had used the "intensive" method of treatment for three years and questioned the statement that it was unsuitable for out-patient treatment. Dr. Bowie and he had employed it routinely for a year and a half before the war in out-patient treatment, and Dr. Bowie was still using it without trouble.

Since the beginning of the war he had treated 1,800 cases of gonorrhœa by this method and had been struck by the contrast in tolerance between in-patients (as military circumstances compel service cases