Uleron, when given by the delayed method, also shortens the disease and is better tolerated than prontosil album. It achieves a permanent-cure rate of 56 per cent., but owing to the delayed method of administration complications were met with in 20 per cent. in this series. The majority of these complications appeared towards the end of the second week—that is, before the administration of uleron.

M & B 693 is well tolerated in the dosage given. It shortens the disease, prevents complications, and produces a permanent-cure rate of 86 per cent. in the cases investigated.

M & B 693 undoubtedly is superior to prontosil album and uleron in the treatment of acute gonococcal urethritis in the male sex.

I wish to express my thanks to Messrs. Bayer Products Ltd. for the supply of uleron and literature and to Messrs. May and Baker for supplies of M & B 693 and literature. My thanks are also due to my medical, nursing, and clerical staffs for their help in this investigation.

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CHEMOTHERAPY OF GONOCOCCAL VULVOVAGINITIS

WITH SPECIAL REFERENCE TO M & B 693

BY

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M & B 693

Working in co-operation with the Venereal Diseases Department, Guy's Hospital, twenty-seven cases of gonococcal vulvovaginitis have been treated with M & B 693 (2-sulphanilyl-aminopyridine) at the Children's Medical Home, Waddon, since May, 1938. The home is for girls from 3 to 14 years suffering from gonorrhoea or congenital syphilis. Most of the cases are referred by the V.D. clinics or hospitals in London, but a few come from the provincial clinics and private practitioners. The ages of the children treated ranged from 3 to 10, and their weights from 2 to 5½ stone. The duration of infection before starting this treatment varied from five days up to five weeks in fifteen acute cases, and from nine weeks up to fifteen months in twelve chronic cases. Four cases had previously received courses of sulphanilamide without benefit, a fifth a course of sulphanilamide and also uleron, and a sixth chronic case had been given M & B 693 before admission, but had relapsed.

Tests at Beginning of Treatment

Gonococci present in urethra and vagina	16 cases
„ „ „ „ „ and rectum	2 „
„ „ „ „ „ vagina	1 case
„ „ „ „ „ rectum	1 „
„ reported in tests at clinics but negative on admission to home	7 cases

The total dose of M & B 693 ranged from 2 to 8 grammes. The first six children to be treated in the home were given 0.5 gramme three times a day, and five of these cases showed symptoms of intolerance. These will be referred to later. The plan followed for the majority (fifteen) of the cases has been to give 0.25 gramme four times daily for four days, making a total course of 4 grammes. Two cases received 1 gramme daily for only three days, a third 1 gramme daily for five days, and a fourth case 1 gramme daily for eight days. A fifth case was given 1.25 grammes daily for four days, and a sixth only 0.5 gramme daily for four days. These children all took the drug well and showed no symptoms of intolerance. The half tablet was crushed, the powder placed on the tongue, and the child washed it down with water. The drug was given after the three meals, breakfast, dinner, and tea, and the last dose at 9 p.m. Precautions taken were the same as for sulphanilamide; sulphur-containing foods—that is, eggs and onions—were excluded from the diet, and no saline aperients were given. Liquid paraffin was prescribed if any aperient was required.

Local Treatment.—Local treatment consisted merely in swabbing the vulva with acriflavine 1 in 1,000 in glycerin, followed by a dermatol dusting powder. This was necessary only for the first few days, and was always discontinued when the course of M & B 693 was completed. In not a single case was any treatment applied to urethra, vagina, or rectum. It is of the greatest advantage to omit local paintings and irrigations, as the habit of masturbation is common in these children, and once acquired it is difficult to break.

RESULTS

With one exception the immediate clinical result was equally good in all cases, but, with the more marked clinical signs, was more dramatic in the acute cases. The acute inflammation of the vulva, vagina, and urethra with profuse purulent discharge cleared up rapidly, and in some cases it was possible to detect signs of improvement after the second dose. In six cases there was no visible pus on the second day of treatment. The remainder were normal on the third, fourth, or fifth day of treatment. It was not practicable to make daily tests in these cases, but with two exceptions all bacteriological reports were negative for gonococci when the first test was made within two to seven days of starting the drug.

The one instance of clinical failure referred to above was an acute case with duration of infection seven days, and tests remained positive for gonococci in urethra, vagina, and rectum. This child through an error had had only 0.5 gramme daily up to a total of 2 grammes, and although a second course of 4 grammes was given she failed to respond. Prontosil album 15 grammes was administered after an interval, but the condition relapsed again nine days after the course was completed. The other case which was not negative at the first test showed "one suspicious pair" on the third day, but was negative when the next test was made on the eighth day and remained so.

OBSERVATION IN THE HOME

In addition to the one complete clinical and bacteriological failure there was an acute case with an excellent immediate response to a course of 4 grammes (that is, no pus from the second day and absence of gonococci when tested on the fourth day) which showed pus again after one week, and gonococci were reported in both urethral and vaginal films. This patient was given a second course of 4 grammes of M & B 693 after a fortnight's interval, and was clinically normal and negative for gonococci on the third day. Four weeks later there was a second clinical and bacteriological relapse. A third course of 4 grammes was given to this patient, and there has been no further clinical sign of infection, and six tests have been negative during a period of seven weeks' observation.

Of the remaining twenty-five cases receiving a single course of M & B 693 seventeen have been watched in the home for thirteen to twenty-eight weeks without showing signs of clinical relapse, and from ten to sixteen negative tests have been made in each case. Eight cases have been watched for three to nine weeks, and three to eleven tests made have been negative. Three cases from the former group would rank as cured according to the generally accepted standard—that is, they have been under observation for six months since completion of treatment with absence of clinical signs of infection, a series of negative films and cultures, a negative complement-fixation test for gonorrhoea, and a final set of tests after an injection of provocative vaccine.

Fourteen of these twenty-five patients have been discharged from the home, and I am indebted to the directors of the clinics to which they have returned for further reports on their condition up to date. Before their discharge they were watched for three up to twenty-eight weeks.

FOLLOW-UP REPORTS FROM CLINICS

Three patients were not required to attend: they had been watched for twenty-seven to twenty-eight weeks in the home and had completed full tests of cure. Two remained well and have been discharged as cured after twenty-six to twenty-eight weeks' observation. Six have remained well and are still attending, bringing the total period of observation up to twenty-two to thirty-two weeks since completion of treatment. Three required further treatment.

It is of interest to study these late failures in greater detail. The first patient had received a course of 6 grammes and had been under observation for seventeen weeks before her discharge from the home. The medical officer of the clinic reported thus on January 6, 1939, on the child's condition as she appeared when arriving at the clinic on September 27, 1938 (eleven days after leaving the home): "Purulent vaginal discharge and much pain and tenderness in left hip-joint. No gonococci found. Pus cells + + +. Coliform organisms grown in culture. Made excellent and rapid progress on local application mercurochrome 10 per cent. and M & B 693 by mouth. No treatment since October 25, 1938. Tests all clear on October 28. All clinical examination clear."

The second and third cases had received courses of 4 and 6 grammes, but had been watched without relapse for only three and eight weeks respectively before leaving the home. Gonococci were reported at the clinic four weeks later. The former case was a chronic infection of one and a half years' duration which had failed to respond to a course of M & B 693 before admission to the home.

There was a possibility of reinfection in the latter case, as a sister was found on examination to be positive for gonococci.

TOLERATION OF THE DRUG

As mentioned above, the first six cases to be treated in the home with M & B 693 were given 0.5 gramme three times daily. Five of these cases showed some signs of intolerance to the drug. One patient vomited three times on the third day, and the drug was discontinued after a total dose of 3.5 grammes. The remaining five cases completed a course of 6 grammes in four days. Three of the children vomited on the second and third days, and one also complained of headache. A fourth had a temperature of 99° on the third evening, but no clinical symptoms were reported and no signs of ascending infection were found. The fifth case showed no symptoms of intolerance. Blood counts were done on the five cases receiving courses of 6 grammes, and a low polymorphonuclear count five days after the course was completed was reported in the case which had the rise of temperature. The child's general health remained good throughout. A blood examination on May 24, 1938, showed: red cells, 4,520,000 per c.mm.; haemoglobin 76 per cent.; colour index, 0.84; white cells, 5,000 per c.mm.—polymorphs 42 per cent., eosinophils 2 per cent., basophils 1 per cent., lymphocytes 36 per cent., hyalines 19 per cent. On July 11 the blood count was: red cells, 4,120,000 per c.mm.; haemoglobin, 76 per cent.; colour index, 0.92; white cells, 5,800 per c.mm.—polymorphs 54 per cent., eosinophils 3 per cent., basophils 1 per cent., lymphocytes 30 per cent., hyalines 12 per cent.

It should be emphasized again that in all further cases in which the small divided doses of 1 gramme daily were taken the toleration to the drug was good, and not one child showed any abnormal symptom.

EXCRETION OF THE DRUG

The urine was tested by a diazo reaction in the first five cases and excretion was found to be rapid. The test was positive in each case while the drug was being taken, and negative twelve and twenty-four hours after completion of the course in four cases. One child showed slight excretion the day following withdrawal of the drug: it is of interest to note that she was the one reported above with the low polymorphonuclear count.

Sulphanilamide

Prontosil album (Bayer) was first used in October, 1936, when, following the work of Dr. Rawlins in the Female Venereal Diseases Clinic, Guy's Hospital, five cases were given 0.45 gramme to 0.9 gramme daily up to a total course of 15 to 40 grammes. With these small individual doses the clinical response was not satisfactory, and gonococci were still present in three cases on completion of treatment. There were no symptoms of intolerance in this short series. These cases are omitted for purposes of comparison with M & B 693.

Trial was next made in August, 1937, of larger daily doses, and fifteen cases were given courses of prontosil album 1.5 grammes or 2 grammes daily in divided doses according to body weight, up to a total of 16.5 grammes to 42 grammes. Four cases in this series showed toxic symptoms which necessitated omission of the drug. They were as follows: two cases had rashes resembling rubella after 16.5 and 20 grammes; one case showed cyanosis after 16.5 grammes; and one case had abdominal pain and slight pyrexia after

17 grammes. A fifth case had severe headache and nausea, but the drug was not omitted and the symptoms cleared.

As a result of the intolerance to the drug, and finding that those children who had received the shorter courses did not show signs of relapse, it has been the practice in the home since November, 1937, to give prontosis album for ten days only. Courses of 0.5 gramme three times daily, to a total of 15 grammes, are given to children under 4 stone in weight, and 0.5 gramme four times daily, total 20 grammes, to children over 4 stone. Sixteen cases have received treatment according to this plan, and there has been only one case of intolerance to the drug. This child showed a heavy morbilliform eruption twenty-four hours after completing a 15-gramme course. The rash faded the following day, but an urticarial eruption developed five days later. This was transitory, fading in a few hours.

Local Treatment.—In addition to the swabbing of the vulva, daily paintings were given to the urethra, vagina, and rectum in most of the cases receiving prontosis album. This was continued for the duration of drug treatment. A vaginal irrigation was also sometimes necessary for the first few days when the discharge was very profuse.

RESULTS

The immediate results of treatment in this series of thirty-one cases with duration of infection from two days to three and a half years were most satisfactory clinically and bacteriologically in twenty-six cases. Fifteen cases remained under observation in the home for not less than six months before they were discharged, and the remaining eleven cases were watched for eight up to twenty-four weeks. There were five failures. Four cases with duration of infection two, seven, seven, and thirty-five days (the last the failed case of M & B 693) remained positive for gonococci. The fifth case showed a purulent vaginal discharge, but gonococci were not reported in films or cultures.

FOLLOW-UP REPORTS FROM CLINICS

Of the fifteen cases completing tests of cure during a minimum of six months' observation in the home, reports have been received on nine cases. The remaining six cases were not required to reattend the clinics by the medical officers. Of the nine cases of which reports have been received, six have been discharged without relapse after a total period of observation of nine to twelve months since completion of treatment; two have remained well and are still attending the clinics, bringing the total period of observation up to ten and thirteen months; and one showed gonococci in urethra and vagina. This last case was the one with a duration of infection of three and a half years. It was known that there was infection in the family.

Three cases remain in the home, having been under observation for eight, sixteen, and twenty-four weeks respectively without relapse.

On the eight cases who were discharged from the home after a period of eight to thirteen weeks' observation the following reports have been received: three cases have been discharged without relapse after a total period of observation of twenty-eight to thirty-five weeks; one has remained well and is still attending after thirteen months' observation; one has remained well and after six months' observation has been transferred to another clinic; and two showed "suspicious pairs" in vaginal films after their

return to the clinics and were given further courses of sulphanilamide. One case defaulted from the clinic: she had been under observation for eight weeks in the home before discharge.

Uleron

A trial supply of uleron was made available in the home by Dr. Oddie of Bayer Products Ltd., and six cases were treated by the "Stoss" method as advised. Uleron 0.5 gramme three times daily for four days, with a total dose of 6 grammes, was given to children under 4 stone in weight, and 0.5 gramme four times daily for four days, with a total dose of 8 grammes, to children over 4 stone.

Three cases responded well, although not so rapidly as those receiving M & B 693 or prontosis album. The first case was given two "Stosses" of 8 grammes each with an interval of three days, the second case two "Stosses" of 6 grammes each with an interval of two weeks, and the third only one "Stoss" of 6 grammes. Before her admission this last case had received a course of pro-septasine, 18.25 grammes, without benefit. Gonococci were present in the urethra and vagina when the course of uleron was given. A test taken on the third day of treatment was negative. These three cases remained satisfactory clinically and bacteriologically and completed full tests of cure until their discharge from the home after twenty-six to twenty-seven weeks' observation.

FOLLOW-UP REPORTS

One patient has been watched at the clinic up to a total of forty-four weeks as there was known to be infection in the parents. She has remained well. The other two children have not been required to attend the clinics. It will be noticed that the length of time these cases are watched after they have been discharged from the home varies in different clinics. It depends, of course, to a certain extent on the presence or absence of infection in other members of the family, but there is no uniform practice as to duration of observation before completion of tests of cure in children. The remaining three cases had failed on sulphanilamide therapy, and uleron was given also without benefit. No symptoms of intolerance to the drug were shown in this small series of six cases.

Comparative Results with the Three Drugs

A comparison of results of treatment is shown in the following table:

TABLE I

	M & B 693	Prontosis Album	Uleron	Total
Number of cases treated ..	27	31	6	64
Immediate failures	2 (7.4%)	5 (16.1%)	3 (50%)	10 (15.6%)
Tests of cure completed in home or clinic; period of observation 6-12 months	5 (18.5%)	15 (48.3%)	2 (33.3%)	22 (34.3%)
Condition satisfactory,* still under observation at clinic	6 (22.2%) (22-32 weeks' observation)	3 (9.7%) (10-13 months' observation)	1 (16.6%) (44 weeks' observation)	10 (15.6%)
Condition satisfactory* for 6 months, transferred to another clinic	—	1 (3.2%)	—	1 (1.6%)
Condition relapsed, still under observation at clinic	3 (11.1%)	3 (9.7%)	—	6 (9.4%)
Defaulted from clinic	—	1 (3.2%)	—	1 (1.6%)
Condition satisfactory,* still remain in home	11 (40.7%) (3-25 weeks' observation)	3 (9.7%) (8-24 weeks' observation)	—	14 (21.8%)

* No gonococci, no discharge.

Comparison between Sulphonamide Therapy and Other Methods

It is of interest to compare, from the figures given in Table II, the present duration and results of sulphonamide therapy with those when other methods were employed in earlier years. The general treatment in the home, covering local hygiene, fresh air with regulated exercise and play, occupation in school, and diet containing plenty of fresh food—that is, milk, butter, and fruit—has remained the same throughout. It has been possible, however, to cut down to twenty-four hours the initial period of rest for the acute cases receiving M & B 693.

TABLE II

No. of Cases	Treatment	Duration of Treatment	Good Results	Relapses or No Response to Treatment
156	Local painting	17 weeks average	103 (65.9%)	53 (33.9%)
36	Oestrin	3–12 weeks	14 (38.9%)	22 (61.1%)
31	Prontosil album	10–21 days	23 (74.1%)	8 (25.8%)
27	M & B 693	4 days	22 (81.4%)	5 (18.5%)

LOCAL PAINTING

The applications used were chiefly mercurochrome 5 to 25 per cent. in glycerin, protargol 10 per cent. in glycerin, neoreargon or acriflavine 1 in 500 or 1 in 1,000. For 156 cases treated from 1931 to 1934 the average duration of treatment was seventeen weeks. Fifty-three cases relapsed while still in the home after suspension of treatment for varying periods, giving a relapse rate of 34 per cent.

OESTRIN THERAPY

During 1935 eleven cases were treated with oestroform (British Drug Houses Ltd.). Daily injections of 200 to 900 units were given up to a total of 5,400 to 43,900 international units during a period of three to ten weeks. The following results were obtained: good response, three cases; immediate failures, two cases; early relapses (seven to sixteen days), four cases; late relapses, two cases.

In 1935 and 1936 twenty-five cases were treated with menformon (Organon Laboratories). Daily doses of 1,000, 2,000, or 3,000 units were given up to a total of 35,000 to 118,000 international units during a period of five to twelve weeks, with these results: good response, eleven cases; immediate failures, two cases; early relapses (three to five weeks), ten cases; late relapses, two cases.

Conclusions

The introduction of sulphonamide compounds marks the greatest advance in the treatment of gonococcal vulvovaginitis.

The duration of treatment has been cut down to only four days for cases receiving courses of M & B 693 and to ten days for cases receiving courses of prontosil album. Perhaps the chief advantage of M & B 693 is that there is no necessity whatever for local treatment apart from merely swabbing the vulva for the first two or three days.

It is possible to judge from the outset if the case will respond to the drug treatment, as improvement is apparent within a few hours in some cases treated with M & B 693, and always within two or three days for both M & B 693 and sulphanilamide.

Discounting the total of ten immediate failures with the three drugs used, there were no relapses in fifty-four cases while the children remained in the home. It is note-

worthy, too, that in no case in which the rectal tests were negative at the beginning of treatment did later infection occur in the rectum. This was a difficulty with the old methods of local and oestrin treatment, when the purulent vaginal discharge remained longer, thus spreading back to the anus and giving rise to infection of the rectum in some cases. From this site reinfection of the vagina followed.

One of the cases treated with prontosil album showed a wart, otherwise no complications developed in this series of sixty-four cases. The incidence of complications is not high in gonococcal vulvovaginitis, as shown in the following table of complications occurring in 467 cases treated at the Children's Medical Home from 1928 to 1936:

Proctitis	.. .. .	55 cases (11.8%)
Cervicitis	.. .. .	11 „ (2.3%)
Endometritis and salpingitis	.. .. .	4 „ (0.8%)
Warts	.. .. .	4 „ (0.8%)
Purulent conjunctivitis (no gonococci found)	.. .. .	4 „ (0.8%)
Tenosynovitis	.. .. .	2 „ (0.4%)
Arthritis	.. .. .	1 case (0.2%)

Urethritis is not counted as a complication, because infection of the urethra is invariably present in gonococcal cases, and the term “vulvovaginitis” does not cover the complete clinical picture.

Summary

Twenty-seven cases of gonococcal vulvovaginitis treated with M & B 693 are reported upon, and also thirty-one cases treated with prontosil album and six cases treated with uleron. Total, sixty-four cases.

Tolerance to these drugs in children is shown to be good when suitable doses are employed for short periods.

The results of treatment were: remained well for five to thirteen months, thirty-four cases; remained well for three to nineteen weeks, fourteen cases; immediate failures, ten cases; late relapses, six cases.

The advantages of M & B 693 over sulphanilamide are shown in the shorter duration of drug treatment and omission of local treatment to the urethra, vagina, and rectum.

Comparison is made of sulphonamide treatment with the methods of local treatment and oestrin therapy as employed in the home in earlier years.

I am pleased to make acknowledgments to Dr. V. E. Lloyd, Director, V.D. Department, Guy's Hospital, for helpful criticism and also for the supply of M & B 693 and for carrying out the urinary diazo tests; to Dr. Morna Rawlins for her interest and advice; and to Dr. F. A. Knott for the blood counts. Examination of all films and cultures and serological tests have been carried out in the V.D. Laboratory, St. Thomas's Hospital, and my thanks are due to Dr. T. E. Osmond.

The annual *Proceedings of the Medical Officers of Schools Association* includes full reports of Sir Kaye Le Fleming's address on the Education of the Body in Public, Secondary, and Preparatory Schools; the late Major Stewart Blackmore's paper on Air Raid Precautions in Public Schools; Dr. J. Lambert's presidential address on the Application of the Recent Epidemiological Advances in Infectious Diseases to Epidemics in Schools; and Dr. Reginald Miller's paper on Epidemics of Vomiting and Diarrhoea in Children of School Age. The headquarters of the Society are at 11, Chandos Street, Cavendish Square, W.1.