TREATMENT OF GONORRHOEA BY M & B 693

BY

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From time immemorial man has sought for the medicine that cures gonorrhoea. The quest was sociological as well as medical. The wish now seems almost to be fulfilled. Whitby (1938a) first directed attention to the new drug, 2-sulphanilyl-amidopyridine (M & B 693), a derivative of the original protosil discovered by Domagk and his assistants. Lloyd, Erskine, and Johnson (1938a) and one of us, F. B. (Bowie, 1938), later noted the early results of its clinical application to gonorrhoea. Since then more evidence has been produced to show that this new preparation must be regarded among the important recent developments in modern campaigns against the gonococcus, if not actually as the most important. More detailed reports by Lloyd *et al.* (1938b), by Prebble (1938), by Batchelor and his co-workers (1938), and by McGregor-Robertson (1938) all indicate that M & B 693 in gonorrhoea is the equivalent of 606 in syphilis. The account now presented contributes further to the highly encouraging reports hitherto published on the action of M & B 693 in gonorrhoea.

General Survey of the Series of Cases

The series under review consists of 127 cases of gonococcal infection in the male treated with M & B 693. Female cases of gonorrhoea occurring throughout the period when these male cases were under observation are not included, as it is deemed advisable that they be observed for a much longer time before any assessment is made of the results of treatment; but preliminary observations in these cases, as in cases of vulvovaginitis and of gonococcal ophthalmia, suggest that results will be analogous.

Of the 127 male cases, 118 were uncomplicated infections of the anterior urethra, and nine showed evidence of more extensive infection. These nine comprised three cases of prostatitis, five of epididymitis, and one of polyarticular arthritis. The duration of infection before treatment with M & B 693 varied from a few hours to over 300 days. Among the anterior uncomplicated cases, treatment was instituted in seventy-nine patients within seven days of the onset of signs and symptoms—in sixty-eight cases within five days; in fourteen cases between eight and fourteen days; in seven between fifteen and twenty-one days; and in eighteen between twenty-two and 315 days. In the nine complicated cases treatment was begun at from fourteen to 154 days from the onset of manifest evidence of the disease, with complications present for from five to ninety-two days. Eighteen of the simple anterior and one of the complicated cases had received treatment before the administration of M & B 693. This previous treatment consisted of urethral lavage with potassium permanganate 1 in 8,000, oral administration of benzylsulphanilamide (proseptasine), sulphanilamide, protosil, and, in one case, intramuscular injection of

gonococcus antitoxin. Twenty-four of those treated with M & B 693 were given, in addition, urethral lavage with potassium permanganate for periods varying from five to fourteen days. All cases were gonococcus-positive at or up to the time of the first dose of M & B 693.

Dosage Employed

As is natural in the use of any new drug, various schemes of dosage were tried at the outset. Seventy-nine of the cases were given 1 gramme thrice daily as the initial dose. The period of maintenance of this initial dose was not fixed, but varied with clinical response, and in most cases was four to five days, after which the dose was reduced to 1.5 grammes daily for a further three to four days. A few patients (eight) were tried on an initial dosage of 0.5 gramme thrice daily, for periods of from six to twenty days in successful cases, longer in others. This reduction in dose was made by way of experiment, but, in view of the obvious superiority of both clinical and bacteriological response to the larger initial dosage, this method was soon abandoned. In another series (seventeen) the initial dose was increased to 1 gramme four times daily for four to five days, then 1 gramme thrice daily for one or two days. Finally, a fourth group (twenty-three) was treated by a more intensive method, consisting of an initial dose of 4 grammes, followed in four hours by 2 grammes, then in another four hours by 1 gramme, and continued at a dose of 1 gramme four-hourly during waking periods, for a total treatment time of three to four days. This intensive treatment is discussed more fully later.

Estimation of Cure

As the standard of the estimation of cure is important in the evaluation of the results of treatment, it is necessary to be somewhat detailed in the conditions which were requisite in this series of cases before patients were regarded as being cured.

After cessation of treatment, by which time the patient was judged likely to be cured, a preliminary period of observation of from three to four weeks, average twenty-five days, was instituted before any tests were applied. During this time it was essential that the particular case be free from any visible or palpable evidence of infection, in that there should be no urethral discharge and no visible pus or debris in the urine and there should be no other recognizable signs of infection in the lower genito-urinary tract. At the end of this interval, provided clinical examination was negative, the first of two tests was given. The test consisted in the passing of the largest sound that would enter the external urinary meatus; massage of the prostate and of the seminal vesicles, with smear examination of the secretion; massage of the anterior urethra; the taking of blood for the gonococcal complement-fixation test; the injection of 1 c.cm. of Parke, Davis's mixed gonococcal vaccine (1 c.cm. containing 500 million polyvalent gonococci); and the instruction to the patient that he must not pass urine for at least three hours after the test. In two to three days the patient returned and was examined for any urethral discharge and for any urinary or other evidence of his infection. The prostate and the seminal vesicles were massaged, and a smear and a culture of the secretion investigated. Any urethral discharge or secretion, and, if doubtful, a centrifuged urinary deposit, were dealt with similarly. Then in four to five days, to complete the week, the patient was re-examined, the same clinical and laboratory procedures being carried out.

After a second observation period of an average of twenty-eight days the second test was applied. This and the subsequent investigations were identical with the first, except that, where the complement-fixation test had already been negative, it was now omitted. As a last measure, one to two weeks

after the completion of the second test the patient was examined by urethroscopy. The usual requirements of clinical and laboratory findings were maintained. Clinically, it was essential that there be freedom from signs and symptoms of gonorrhoea. From the laboratory point of view, smears and cultures were free from gonococci; smears were free from pus cells, except an occasional leucocyte in prostatic slides; and the gonococcal complement-fixation test was negative, or, if previously positive, finally negative.

The standard of cure rested, therefore, on two clinically negative periods of observation and on two examinations and two tests of cure, each test completed by two further examinations. The first and second tests were made at an average of twenty-five and sixty days respectively, and completed at an average of thirty-two and sixty-seven days respectively; while the final observation, urethroscopy, was performed on an average of seventy-four days from the cessation of treatment. The sum total thus consisted of at least seven investigations over an average period of from three and a half weeks to two and a half months from the termination of treatment. One group of eight patients passed satisfactorily the first of the tests of cure, but did not undergo the second. According to the standard of double tests, such cases were technically defaulters; but when it is realized that the single test in itself is regarded

when they were given, but did not complete, first tests of cure. The remainder were definitely doubtful, defaulting at various periods up to forty-two days from the completion of treatment. So far no patient of this group has indicated, by letter or by return to the clinic, the possibility of the persistence of infection.

Transferred.—Five cases, or 3.9 per cent., all of anterior urethritis, were transferred to other clinics or to the care of their own doctors, having first remained clinically and bacteriologically free from infection up to seven days from cessation of treatment.

Resistant.—Six patients, or 4.7 per cent. of the series, did not respond, other than temporarily—two not even temporarily—to M & B 693. These cases are dealt with later.

The total number of defaulters—that is, those who did not complete the original standard of two tests—was twenty-five (19.7 per cent.). This is really not a high rate in view of the fact that eight of these (technically) defaulters passed a substantial test of cure, leaving seventeen cases (13.4 per cent.) of real defaulters, and here again, there are possible cured cases. Among those transferred there may be other successes. The institution of double tests of cure was, and probably will be, a severe strain on the loyalty of the patient, who, because of anxiety to escape from the clinic as soon as possible on account of

TABLE I.—Showing Results of Various Initial Dosage Groups in 127 Cases

Initial Dosage Groups	No. of Cases	Results, showing Numbers of Cases, Average Total Dosage, and Average Duration of Treatment														
		Cured; Passed Two Tests			Probably Cured; Passed One Test			Doubtful			Transferred			Resistant		
		Cases	Gm.	Days	Cases	Gm.	Days	Cases	Gm.	Days	Cases	Gm.	Days	Cases	Gm.	Days
0.5 gm. t.i.d. . . .	8	5	17.3	10.4	—	—	—	—	—	—	1	22.5	15	2	68.2	28
1 gm. t.i.d. . . .	79	56	18.8	7.9	5	24.7	10.2	13	23.5	10	3	16.3	8.3	2	36.2	19.7
1 gm. q.i.d. . . .	17	10	16.3	5	2	18.5	5	2	18.5	5	1	16	5	2	41.5	16.6
4-2-1 gm. . . .	23	20	20.1	4.1	1	14	2	2	9	2	—	—	—	—	—	—
Totals	127	91			8			17			5			6		

as sufficient by some workers, with perhaps the proviso that a longer period between cessation of treatment and test of cure is advisable, it is likely, in view of the general trend of results, that these cases were also cured. It may be of some significance that among those who passed double tests of cure none failed in the first test.

Details of Results of Treatment

The results of treatment are classified under the following groups: cured, probably cured, doubtful, transferred, and resistant cases. Table I shows, in addition to dosages, the results of M & B 693 therapy generally.

Cured.—Ninety-one patients, or 71.7 per cent. of all cases treated, consisting of eighty-seven cases of anterior urethritis, one of prostatitis, two of epididymitis, and one of poly-articular arthritis, passed double tests of cure.

Probably Cured.—Eight patients, or 6.3 per cent. of the whole, passed one test. These comprised seven cases of anterior urethritis and one of epididymitis. The probabilities of cure have already been mentioned.

Doubtful.—Such cases numbered seventeen, or 13.4 per cent. of all, and were made up of fourteen cases of anterior urethritis, two of prostatitis, and one of epididymitis. Details of individual cases are not necessary. Suffice it to state that all defaulted before they could be placed in a more satisfactory category of results. Two (mentioned under "Relapses") actually passed one test of cure, but, because of histories of relapse or, more likely, of reinfections, were not included in those probably cured. Four others arrived at the stage

fears of ultimate discovery and exposure, or who, because of being resident in some rural area from which attendance is irksome, finds it difficult to reconcile the necessity for multiple examinations over a prolonged period with what was apparently a simple infection cured in a few days, merely by swallowing a few tablets. Adequate follow-up control, however, is of great importance, and is a point to be remembered by all those who would employ M & B 693 in the treatment of gonorrhoea.

Relapses or Reinfections

Relapses, or possibly reinfections, occurred during treatment or subsequent to the conclusion of treatment in seven cases. One was a patient on the lowest dosage of 0.5 gramme thrice daily. After being gonococcus-negative on the second and third days, he relapsed while under treatment, and showed gonococci from the tenth to the fourteenth day, thereafter becoming permanently negative. Six other cases relapsed or were reinfected at intervals of from six to fifty days after the termination of treatment. Actually in all six exposure to possible infection was admitted, in one case with the original source of infection—a woman who could not be prevailed upon to visit the clinic. To all six cases further treatment was given. Four were ultimately classified as cured. A fifth and a sixth passed one test of cure quite satisfactorily, but, because of their histories, are placed with the seventh—a defaulter after cessation of treatment—in the group of doubtful cases.

Cases Resistant or Responding only Temporarily to M & B 693

It is hardly to be expected that out of 127 cases there should not be any who would not respond to treatment. Six failed to do so other than temporarily. Some details of these are set forth in Table II.

TABLE II.—Cases Resistant or Responding only Temporarily to M & B 693

Case	Type of Case	Duration of Disease	Treatment by M & B 693				Response later to
			Initial Dosage	Total Dosage	No. of Courses	Total Time	
1	Ant. ureth.	4 days	0.5 gm. t.i.d.	35 gm.	1	21 days	Sulphanilamide
2	"	12 "	"	101 gm.	5	35 days	Urethral lavage
3	"	1 day	1 gm. t.i.d.	43 gm.	1	15 days	" "
4	"	4 days	"	51 gm.	2	14 days	" "
5	"	2 "	"	26 gm.	2	7 days	Sulphanilamide and urethral lavage
6	Epidid.	7 "	1 gm. q.i.d.	41 gm.	2	11 days	" "

Objection may be taken to Case 5 of the series, a patient who had only seven days' treatment; but he received 14 grammes over five days at the rate of 1 gramme thrice daily and relapsed, and then 12 grammes at an intensive rate over two days and again relapsed. Experience by then was beginning to indicate that in such cases the principle of ringing the changes could be employed with profit, and the treatment by M & B 693 was terminated and another substituted.

Should Treatment by M & B 693 be Delayed till Immunity Develops?

Whatever may be the outcome of opinion regarding the advisability or otherwise of suitable delay in the use of other members of the sulphonamide group in the treatment of gonorrhoea, there seems to be little evidence so far of any divergence of view as to what should be the procedure in the case of M & B 693.

Lloyd *et al.* (1938b) write: "Many must consider, as we do, that the deliberate imposition of a delay period in the early and highly infectious stage is likely to be dangerous. There are many undesirable factors associated with such delay: the anxiety of the patient at the persistence of symptoms, the infectivity of the discharge, the approach of the danger period for complications, the likelihood of patients defaulting—all these are of great importance and render the control of the disease an objective to be attained at the earliest possible moment. The desirable chemotherapeutic agent is one that can be used with effect at the earliest stage of the disease, and we consider that the introduction of M & B 693 fulfils this requirement." Prebble (1938) states that "it therefore appears advisable to start treatment right away with irrigation and with M & B 693." Batchelor *et al.* (1938) consider that "there is no necessity to wait for immunity to develop; M & B 693 should be given as soon as the diagnosis is made." McGregor-Robertson (1938) is of the opinion that "delay in starting treatment is unnecessary and undesirable."

The question is one which may yet have to be answered in final terms of more adequate data, but so far as our experience goes we have no hesitation in stating that M & B 693 should be administered at the earliest possible moment. There is more to be considered than the mere fact that one form of treatment may give results slightly superior to those of another. Venereal disease, including

gonorrhoea, is unfortunately not always confined to the individual, but is apt to spread; and, results being equal, or approximately equal, that treatment which takes effect at any stage of an infection, but particularly in the early stages, is always to be preferred. Table III gives the details of eighty-nine cured cases, divided according to whether treatment was begun within seven days or later than one week from the onset of signs and symptoms.

TABLE III.—Showing the Average Time, in Days, for Eighty-nine* Cured Cases to become Gonococcus-negative (Sixty-one Treated during the First Week of Disease and Twenty-eight Afterwards)

Initial Dosage	No. of Cases	Treatment During 1st Week		Treatment After 1st Week	
		Cases	Gc.-neg. in	Cases	Gc.-neg. in
0.5 gm. t.i.d. ..	5	2	9.0 days	3	7.7 days
1 gm. t.i.d. ..	54	38	2.4 "	16	2.4 "
1 gm. q.i.d. ..	10	6	1.5 "	4	3.0 "
4-2-1 gm. ..	20	15	2.1 "	5	1.8 "

* The total number of cured cases was ninety-one, but two—one in each group of the 1 gm. t.i.d. division—are omitted because of irregularity in observation rendering assessment of response difficult.

Other cases, not included in Table III but treated with M & B 693, totalled thirty patients—eight probably cured, seventeen doubtful, and five transferred. Taking these together, irrespective of initial dosage, the results were:

Treated before 7th day—14 cases: Average time to become gonococcus-negative, 2.1 days.

Treated after 7th day—16 cases: Average time to become gonococcus-negative, 3.5 days.

In the case of the six resistant patients the duration of infection before treatment varied from one to twelve days, average five days. There is thus little difference between the results of early and delayed treatment. It may be stated that these figures are probably somewhat in excess of what actually occurred. Because of the considerable proportion of seafaring and of rural patients among those treated, it was not possible to see all patients daily in the early stages of treatment, and some may have become negative before the actual entry to this effect in their respective case-sheets. Taken all over, treatment begun up to the end of the first week gave results slightly superior to those of treatment instituted after the seventh day. In view, however, of the general considerations of management of gonorrhoea, there is no doubt as to which is the more desirable method.

M & B 693 Alone v. M & B 693 plus Urethral Lavage

Another point which remains to be decided is whether optimum results may be achieved with M & B 693 alone or whether the addition of urethral lavage is essential. Lloyd *et al.* (1938b) do not differentiate between the two. Prebble (1938) considers the combination of M & B 693 and lavage to be the better method. McGregor-Robertson (1938) indicates that irrigation increases the efficiency of the oral method. Batchelor *et al.* (1938) state that "no irrigations or other adjuvant treatments are necessary." Irrigations in our series were given "mainly for psychological reasons" (Bowie, 1938) throughout the transitional stage between the old method of treatment by lavage and the new mode of oral therapy. Only twenty-four such patients received urethral lavage (potassium permanganate 1 in 8,000). The number is too small to be of significance by comparison, particularly if subdivisions be made into M & B 693 dosage groups. There was no difference in the time taken by cases to become gonococcus-negative. Actually the duration of treatment was longer in those

on lavage than in the case of those on M & B 693 alone; but no real opinion can be given, as this was the trial stage of various doses and of various durations of treatment by M & B 693. On the other hand, there is no reason to suppose that lavage would enhance the final results. The fact that three of six resistant cases later responded to lavage alone, and two to lavage plus sulphanilamide, might be indicative of the advisability of lavage as a routine measure. But there will always be exceptions, and it is probably safe to assert that the abolition of lavage as a routine would be to the advantage of all concerned—those suffering from gonorrhoea and those engaged in treating it. The excellent results of M & B 693 alone certainly do not call as yet for any revision of our opinion that there does not seem to be any necessity for the at least wearisome, if not at times harmful, rites of urethral lavage.

Complications

Before Treatment.—Nine cases had developed complications before treatment. It is always difficult to estimate when any complication has resolved, as, apart from clinical opinion, an apparent physical resolution does not necessarily mean a bacteriological cure. So far as could be judged, three cases of prostatitis resolved in from five to fourteen days; four cases of epididymitis recovered in from six to fourteen days; and one case of polyarticular arthritis was free from all disabilities by four to five weeks. (Another case, of epididymitis, fell into the resistant group.)

During Treatment.—The foregoing results, however, are of less importance than another feature of the effect of M & B 693. One of the great attributes of this drug is the remarkable absence of complications in cases where it has been exhibited before the onset of the danger period. Complications subsequent to treatment developed in two cases only, and these were in the resistant group. In all the other groups, totalling among them 121 cases, not one complication was found. The two instances noted were one of peri-urethral abscess and one of epididymitis.

Toxic Reactions

The incidence of toxic manifestations was related to the dosage—not so much the length of treatment as the intensity of treatment. Table IV shows the distribution of toxicity in relation to amounts given. The comparative degrees of mild and severe were assessed from information supplied from patients, and, as is natural under such conditions, are of approximate accuracy.

TABLE IV.—*Incidence of Minor Toxic Reactions in 127 Cases, Classified into Mild and Severe Degrees*

Initial Dosage	No. of Cases	Mild Degrees		Severe Degrees	
		No.	Per cent.	No.	Per cent.
0.5 gm. t.i.d. ..	8	2	25	0	0
1 gm. t.i.d. ..	79	24	30.4	5	6.3
1 gm. q.i.d. ..	17	11	64.7	1	5.9
4-2-1 gm. ...	23	13	56.5*	5	21.7*

* This high incidence was found only during the first twenty-four hours of treatment.

Generally speaking, the higher the daily dosage the greater the incidence of toxic reactions. That of the third group, 1 gramme four times daily, is unexpectedly high. This was actually the minimum dosage at which treatment was maintained in the fourth, or 4-2-1 gramme, group: in this latter group a high proportion of toxic manifestations was recorded during the first twenty-four hours of

treatment; then the general incidence fell to that, roughly, of the second, or 1 gramme thrice daily, group. It may be that in the smaller number of the third group a proportionally higher incidence of reactions occurred by chance. Further reference to the toxic effects in the 4-2-1 gramme group is made later on. A point worthy of comment is that at the rate of 1 gramme thrice daily the number showing toxic effects did not exceed 37 per cent. The side-effects noted were: drowsiness, lassitude, general sense of malaise with no complaint in particular, headache, nausea, vomiting, insomnia, generalized pruritus, dyspnoea with mild methaemoglobinaemia (two cases), mild cyanosis, and sweating at night. No rashes occurred in this series, though in two female cases at present under observation a generalized scarlatiniform eruption developed, in one case mostly on exposed areas. None of the more serious toxic effects was encountered. Though as yet there is no effective method of completely neutralizing toxic results, a noticeable feature was their transient nature, subsiding rapidly as they did on withdrawal of the drug.

Intensive Treatment

For some time an intensive form of treatment has been in operation in roughly every second male case of gonorrhoea. Twenty-three cases of such treatment are included in this series.

The method is referred to in the clinic as the "8-4-2" treatment, styled in tablets (of 0.5 gramme) instead of grammes, as a patient naturally counts his dosage in tablets. Up till now this treatment has been confined to those within easy reach of the clinic, in case any necessity arose for re-attending before the time fixed for the next examination. Under this system the patient is made to swallow eight tablets (4 grammes) on the spot—that is, before he leaves the examination room. He is then given detailed instructions regarding general considerations of behaviour, including the special precautions in taking drugs of the sulphonamide group, and is told to take four tablets (2 grammes) in another four hours; then, at four-hourly intervals during waking hours, two tablets (1 gramme), until the end of a period of roughly seventy-two hours from the beginning of treatment. Modifications of dosage develop as a matter of course, depending upon whether treatment be started in the morning or in the evening; but as a rule the actual amounts of M & B 693 taken aggregate from 6 to 8 grammes on the first day and from 4 to 6 grammes on the second and third days. Treatment may be prolonged for another day or so at the same rate or at a lower rate of 1 gramme thrice daily, depending more on the clinical response (freedom from discharge) than on the bacteriological results. In several of these cases it was noted that a small mucoid bead was expressible from the urethra on the day on which treatment was terminated. In this secretion gonococci were still present, but by the following day, without further administration of M & B 693, all trace of discharge had disappeared, and the cases subsequently remained completely negative, both clinically and bacteriologically. These observations suggest confirmation in the clinical field of the experimental findings of a "lag" phenomenon in the mode of action of M & B 693 (Whitby, 1938b).

It is not claimed that this may be the best or even the most desirable form of treatment, but it does appear to merit further trial; and from an opinion expressed by Whitby (1938b), and from our clinical experience, two considerations are important: the first is that sulphonamides, on the whole, perform their work either speedily and efficiently or slowly and imperfectly; the other is that the major, or dangerous, toxic effects are more likely to arise from prolonged treatment than from brief treatment.

Against the use of the 8-4-2 tablet (4-2-1 gramme) scheme, of usually from three to four days' duration, is the initial high incidence of toxic reactions—78 per cent. of cases. Only roughly 22 per cent. of these were severe in degree, the remaining 56 per cent. being mild. Details are given in Table IV, but, in addition to the information supplied there, it may be repeated that the high initial incidence of toxicity lasted merely for twelve to twenty-four hours, after which it dropped to that found in the 1 gramme thrice daily dosage, in which the general incidence of toxicity was only 37 per cent. This transient state of malaise was probably no greater than that experienced by most of the patients during the twenty-four hours subsequent to the general conditions of dissipation leading to infection. As yet, toxic manifestations, even if severe, have all been of the minor varieties, and repeated blood examinations have so far failed to indicate any necessity to abandon this technique.

In favour of the 4-2-1 gramme method are several considerations. In the series of twenty-three cases so treated, twenty were cured, one probably cured, and one of the remaining two passed the first test of cure, but because of a relapse, admittedly a possible reinfection, was classified with the other as being doubtful. No instance of resistance was noted, while in 104 other cases six such failures occurred. These figures may be too small to be of great importance, but there are at least theoretical advantages to be considered. It is reasonable to assume that an abrupt intensive attack will always mean a more swiftly deleterious effect upon the gonococcus, by which attack the infection may be eradicated more quickly and efficiently, and by which may be avoided the development of what may yet become known as M & B 693 resistance. Further, as has already been suggested, the avoidance of serious toxic results may possibly be effected more by short rigorous treatment than by prolonged, though milder, methods. Finally, it is a point worth knowing that, if necessity arises, a man may be cured of gonorrhoea by treatment lasting only three days, or even less!

Comments

That M & B 693 is a remarkable drug cannot be questioned. What may be, and probably will be, debated for some time is how best to employ it: early during gonorrhoea or later on in the disease; in short intensive courses, single or multiple, or by more prolonged easy-going methods; with or without urethral lavage, or perhaps with or in alternation with some other forms of adjuvant treatment yet to be devised; how long it should be given to apparently resistant cases before trying some other method of treatment, and so on. It may be pertinent here again to quote Whitby (1938b):

"The effect in gonorrhoea must also be remembered: in many cases dramatic and instant cure; in others, a recrudescence of the infection, which is then resistant to drug treatment or at least to treatment with the same drug, but which may respond to a change of compound. And I have already indicated that M & B 693 appeared to become more progressively inactive on *Streptococcus viridans*. This is highly suggestive that resistant or insensitive individuals may be developed. It gives a hint for the clinical field—that is, that if the first course of a drug is not completely successful it might be as well to use a different drug for a second course."

The great bulk of cases may be cured by a total dosage of from 15 to 20 grammes. The majority may also be cured within a week. It is probably advisable to avoid anything less than 3 grammes daily as the initial dosage in treatment. In initial amounts above this, in degrees short of undesirable toxicity, it may yet be established

that the higher the initial dose the speedier may be the cure, the greater the proportion of cures, and, notwithstanding a high incidence of minor toxic reactions for a short period, the greater may be the immunity from major or serious reactions. Though female cases are not included in this report, for reasons already stated, mention may be made of the fact that, as a rule, they are less tolerant than men to M & B 693. Children, on the other hand, appear, with comparative doses, to have the greatest tolerance of all.

For how long one should persist in the presence of positive bacteriological findings is a difficult matter to decide. The suggestion is made that if a patient does not become gonococcus-negative by the end of a week, particularly if his dosage has been fairly high, or if he relapses more than once, a change to some other member of the sulphonamide group should be considered. It is doubtful if even a return to M & B 693 after some time is advisable.

One great point to be remembered is that the cessation or the apparent cessation of discharge is not necessarily synonymous with cure. Those who are not prepared to follow up their patients to a reasonable estimation of cure should note this: an optimistic patient may be excused for believing that the disappearance of his discharge means cure, but his doctor should not also be tricked into the same blunder, for even M & B 693 is not infallible. Whatever the apparent results are, care should be taken, by adequate investigation and observation, to ensure that cure has really been effected. The very efficacy of a drug like M & B 693 may prove to be not altogether an unmixed blessing, in that it may incite a high defaulting rate among patients. The high incidence of cure may lead some to assume such a state of affairs too readily, and to neglect corroboration of the assumption. It appears to be advisable to evolve a reasonably efficient estimation of cure without prolonging tests unnecessarily—especially to a degree where the patient, if he does not default, now attends with his tongue in his cheek, in the meantime having reverted to his former sexual activities.

A most important aspect of M & B 693 is its efficiency in preventing what makes gonorrhoea a serious disease—the development of complications. As already mentioned, apart from two cases among the six which did not respond to the drug, not a single complication developed in our series. This highly protective action must surely be one of the most potent of all arguments concerning the relative values of early and late treatment.

Summary

Treatment of a series of 127 cases of gonorrhoea in the male by M & B 693 is described.

The standard of cure insisted upon is detailed.

Thirty patients in this series ceased to attend, or were transferred to other centres, before final tests of cure could be carried out. Of the remaining ninety-seven there were ninety-one patients who passed all tests of cure—which gives over 93 per cent. of successful results. There were six failures.

Of those ceasing attendance, eight were probably cured, seventeen were doubtful, and five transferred.

Toxic reactions encountered were of the minor type, varying in incidence with the dosage employed. These reactions subsided rapidly on withdrawal of the drug, and no major toxic effects have developed.

Various dosage schemes have been tried, and it is suggested that intensive treatment over a short period merits further investigation.

Treatment should be instituted at the earliest possible moment, particularly in view of the noteworthy absence of complications in cases so treated.

In face of failure to respond within a week, or of early relapse, persistence with M & B 693, even in repeated courses, has proved ineffective. In the interests of the patient, in such circumstances, resort should be made to some other form of therapy.

In our experience M & B 693 has proved the most effective therapeutic agent yet introduced in the treatment of gonorrhoea.

We wish to thank Dr. John Smith, director of the City Hospital Laboratory, Aberdeen, for his co-operation in this investigation. We desire also to express our thanks to Pharmaceutical Specialities (May & Baker) Ltd. for generous supplies of M & B 693 over the trial period of this study.

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SULPHANILAMIDE IN THE TREATMENT OF MEASLES*

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There is now a considerable literature regarding the value of sulphanilamide in the prevention and treatment of certain streptococcal infections. The investigation of its value in the treatment of measles, in which many of the complications are of streptococcal origin, is therefore important, and such an investigation was carried out during the 1937-8 epidemic in Glasgow. A ward in Ruchill Hospital was allocated for the purpose, and this report is based on the cases admitted to that ward between December, 1937, and March, 1938. There was no selection of patients, the ward taking its normal part in the reception of such cases of measles as were admitted to hospital. The material may therefore be regarded as representative of the disease in this district during the period reviewed. There is, of course, some selection of cases outside of hospital, so that a high proportion of complicated cases is admitted. The patients were under my own control throughout.

Plan of Investigation

The cases were allocated, in order of admission, alternately, to two groups. The first, or control group, received the usual nursing and expectant medical treatment; the second group received in addition sulphanilamide (para-aminobenzenesulphonamide). The dosage of the drug was varied with the age of the patient: under 5 years, 0.25 gramme was administered at four-hourly intervals for a

period of ten days, followed by 0.25 gramme thrice daily until dismissal; those over 5 years received 0.5 gramme at the same intervals and for a like period. (This dosage was similar to that which had been used with benefit in cases of erysipelas. While no serious ill effects were noted from the use of the drug, five cases showed moderate cyanosis and one case drug fever.) Apart from this the two groups received strictly comparable treatment. All cases were given on admission 4,000 units of diphtheria antitoxin as a prophylactic procedure. The control group numbered sixty-two, and those treated with sulphanilamide sixty-three, a total of 125 cases. The additional case in the treated group is explained by the removal from the control group of a case in which the diagnosis of measles was not confirmed.

Method of Assessment

Each case was examined on admission and a note made of the presence of any complication. It was decided that information regarding the value of the drug would be best obtained by comparing the two groups with respect to the following criteria: (i) the duration, in days, of primary pyrexia; (ii) the duration, in days, till clinical cure of complications noted on admission; (iii) the incidence and nature of complications arising in hospital; (iv) the duration, in days, till clinical cure of complications arising in hospital; (v) the duration, in days, of residence in hospital. All cases were therefore reviewed and examined daily and notes were made of their progress, with special reference to the above points. For the purpose of the experiment the day on which the rash appeared was regarded as the first day of the disease.

Before recording the results it is necessary to compare the two groups with respect to factors which might influence them. The most important of these are: (1) the age and sex distribution, (2) the duration of the disease before admission to hospital, and (3) the incidence of complications noted on admission. Tables I, II, and III show that the two groups were fairly evenly balanced in these respects, except that the cases receiving sulphanilamide treatment showed a slightly higher incidence of complications on admission.

Measles

TABLE I.—Age and Sex Distribution

Age Group (Years)	Control Group		Sulphanilamide Group	
	Males	Females	Males	Females
0-1	4	5	8	7
1-2	13	9	9	8
2-3	7	4	8	2
3-4	2	3	5	4
4-5	3	4	2	1
Over 5	1	7	3	6
Totals	30	32	35	28

TABLE II.—Duration of Illness (in Days) before Admission

Days:	0	1	2	3	4	5	6	7	8-14	Over 14
Control Group	3	12	7	9	3	8	4	4	9	3
Sulphanilamide Group	7	11	12	5	6	4	4	3	9	2

* A report to the Therapeutic Trials Committee of the Medical Research Council.