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FURTHER NOTES ON THE TREATMENT OF GONORRHŒA WITH THE SULPHONAMIDE GROUP OF DRUGS.

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IN a previous article in this Journal, written in July, 1938 (Winter, 1939), the author described his findings after a year's work with the sulphonamide group of drugs in the treatment of gonorrhœa. This work has continued and, after a further year, it is considered that sufficient data has now been accumulated to justify the formulating of a routine method for the treatment of this disease.

During the past year, the majority of cases have been treated with sulphanilamide and M & B 693, but small quantities of albucid and streptocide have also been tried. In the case of both the latter drugs, results were disappointing. In the present article, for the sake of brevity, the drugs will be referred to under two headings—"Sulphonamide" and "M & B 693."

M & B 693 is undoubtedly the drug of choice in any stage of the disease, and has the great advantage of being equally therapeutically efficient even in the very earliest stages. The sulphonamides are effective only if withheld for at least ten days to allow of the development of some degree of immunity, at which stage they have almost equal therapeutic value; this, however, means increased hospitalization. As against this objection, many hospitals and medical stores hold large stocks of these latter drugs which, incidentally, are only about a quarter of the price of M & B 693; they could, therefore, be used for the treatment of gonorrhœa in the absence of supplies of M & B 693 or until surplus stocks of the sulphonamides were used up, provided that the method of administration described below is followed.

These findings are in agreement with Cokkinis (1939), who states that M & B 693 is 1·8 times more potent in gonorrhœa than the sulphonamides, and that the latter drugs do not cure a high percentage in the first week but that a big change for the better takes place in the second week. Uleron is still weaker and therefore requires a still higher degree of immunity. He places the drugs in the following order :—

Treatment of the patient in the first week : M & B 693.
Treatment of the patient in the second week : Sulphonamide.
Treatment of the patient in the third week : Uleron.

The following further facts have come to light during the present trials :—

(1) Complement-deviation tests were done before treatment, seven days after commencement of treatment, and one month after cessation. Sulphonamide treatment was quite definitely most effective in those cases in which this test was positive at the commencement. With M & B 693, it did not appear to matter whether the test was positive or negative. This test is consequently a valuable indicator in treatment with the sulphonamides. Hartung (1938) came to a similar conclusion regarding the complement-deviation test when working with uleron. This observer found that the test became positive in the majority of uncomplicated cases after about a fortnight and increased thereafter—earlier in cases in which complications developed. He further found that the results of treatment were invariably better in patients showing a positive reaction. In the series under review, moreover, it was found that cases with a previous history of gonorrhœa in the last one or two years did well on both M & B 693 and sulphonamide.

(2) In the earlier cases treated with sulphonamide (Methods 17 and 18) vaccine in full doses was given as preliminary treatment in an endeavour to raise immunity before the administration of the drug. These cases did not do so well on the whole as those which received no preliminary treatment. Later, following Hartung (1938), who observed that large doses of vaccine, sufficient to produce a feverish reaction, caused a positive complement-deviation test to become negative again, subcurative doses only were given (about half or less of the normal dose) ; results were very much better (Method 20). In a few cases patients were given a bottle of beer a day as part of the preliminary treatment in an endeavour, deliberately, to increase the severity of the disease ; it had been observed that cases with the most copious mucopurulent urethral discharge, swarming with gonococci, did best under subsequent treatment.

(3) Total white blood-cell counts were made before treatment, on the third day after commencement of treatment and on the completion of treatment. In the case of sulphonamide, it was found that the patients who showed a mild leucocytosis, in the neighbourhood of 10,000 per c.c., which dropped by at least 20 per cent to round about 8,000 or less by the third day, did well. Cases in which the initial count was normal, or only slightly raised, and in which there was little or no drop, or even a rise, on the third day, did not respond to treatment. With M & B 693, the drop on the third day was

even more marked in the majority of cases, but an absence of initial leucocytosis or drop during treatment did not appear to bear any relation to the therapeutic result. In view of the shortness of the course (four days only), blood examination is of little or no value in predicting possible toxic effects.

(4) Forgan (1939) casts some doubt as to the advantage of restricting sulphur intake during treatment. A number of cases were left on ordinary diet whilst taking large doses and came to no harm.

(5) Recent work has shown that these drugs are not absorbed by the stomach but by the small intestine, and that concentration in the blood reaches a maximum in three hours, falling to zero in twenty-four hours. Concentration in the cerebrospinal fluid is as great as in the blood. Excretion is in the urine. Rate of elimination is independent of the plasma level but follows urine flow ; the drug is apparently filtered out by the glomeruli but 70 to 80 per cent is reabsorbed by the tubules. M & B 693 is absorbed slightly more slowly than sulphonamide. Absorption of both is facilitated by the administration of sodium bicarbonate or dilute hydrochloric acid (Buttle, 1939). It therefore follows that to obtain optimum therapeutic effect, the drug should be given in conjunction with sodium bicarbonate and the fluid intake should be restricted during treatment, although Lloyd (1939) suggests that such restriction may lead to intolerance ; no cases of intolerance from this cause were noted in the present series. Toxic effects can be combated by increase in the fluid intake and by diuresis ; administration of sodium bicarbonate in cases of gastric disturbance does not benefit the condition as it only facilitates further absorption of the drug (Buttle, 1939).

(6) Most observers agree that it is essential to maintain a high concentration in the blood for short periods. Low dosage, often for several weeks, is not only therapeutically useless but renders the patient resistant to further treatment, possibly by stimulating the liver to detoxicate larger quantities of the drug (Lloyd, 1939). The best results are obtained when the concentration in the blood is quickly raised to a high level—5 or more mgm. per cent, equivalent to 3 to 5 gramme doses daily (Lloyd, 1939). These findings are borne out by observers in the United States of America (Venereal Diseases Information, 1938) who advocate large doses, contending that symptoms necessitating discontinuance are not frequent enough to constitute serious limitations ; with doses of 6 to 8 grammes per diem, they claim 70 to 80 per cent cures. They further state that with smaller doses results are less definite (cures only 45 to 75 per cent), and that symptomatic cure only is obtained with possible formation of the carrier state. Concentration in the blood falls during the night and it has been suggested (Forgan, 1939) that the drug acts as a food and that gastric symptoms are a form of night starvation. In the series under review, marked improvement resulted when patients were given an extra dose at midnight (Method 26). The best results were obtained in the present series when a large initial dose (4 tablets

= 2 grammes) was given, followed by 2 tablets (= 1 gramme) two-hourly and a further dose of 1 gramme at midnight (Method 26).

(7) Toxic manifestations were all of a relatively mild nature and could, with safety, in the majority of cases be disregarded ; if more severe, they disappeared promptly on discontinuance of the drug for twenty-four hours and the exhibition of copious fluids. Chief amongst these toxic reactions were nausea, vomiting, abdominal pain, diarrhœa, headache, dizziness, and mental dullness. A few patients developed cyanosis which was looked on as of no consequence in view of Buttle's (1939) contention that this is partly due to elaboration of pigments. Gastric symptoms were slightly less in evidence after the midnight dose was introduced, thus bearing out Forgan's (1939) contention referred to above. Drug fever occurred in one or two cases and in one it was particularly definite. All rashes noted were of the morbilliform or of the scarlatiniform type ; none of them was very severe. No bullous eruptions as described by Simon (1939) were observed. With a view to testing the photosensitizing action of these drugs, as described by Newman and Sharlit (1937), Erskine (1939), Hallam (1939), and other observers, a number of cases who were taking large doses of M & B 693 were allowed to sun-bathe in the Hills in India at midsummer until they were well sun-tanned ; in no case was light-sensitiveness apparent.

American observers (Long, 1939) report cases of "acetyl-sulfapyridine stone" formation in the kidneys with hæmaturia, anuria, and nitrogen retention in some instances amongst cases under treatment with "sulfapyridine." None of the cases under treatment in the present series has so far developed any symptoms of this nature.

(8) In the series, two cases were particularly resistant to both sulphonamide and M & B 693 ; they eventually reacted only to prolonged local treatment. In such cases, which are apparently sulphonamide-resistant, there is no advantage to be gained in persevering with treatment by these drugs. In these cases there was strong suspicion which, unfortunately, could not be sustained, that the patients, who were nursing orderlies, had been practising self-treatment with small doses of the drug for some time before reporting sick.

(9) Therapeutic results are so encouraging in the early stages of the disease under treatment with M & B 693 that it is suggested that prophylactic use of this drug might be seriously considered. Lloyd (1939) suggests its use as a prophylactic but states that so far it has not been so used although, experimentally, it has been a successful prophylactic in mice. It is suggested that a supply of tablets might be issued to the preventive ablution centres of one or more selected units ; issues to individuals to be controlled by means of a carefully kept register. Suggested prophylactic dosage is 4 tablets (2 grammes) at once, followed by 2 tablets (1 gramme) in four hours or at reveille next morning.

The following routine treatment courses are recommended :—

M & B 693 (*for choice*).—May be commenced on the first day of the

disease. Restriction in diet (avoidance of eggs, onions, etc.) is advisable but not essential; it is a good plan to give glucose barley sugar during treatment, to protect the liver. Restriction in fluid intake is important. There is no advantage in doing either a complement-deviation test or a total white blood-count. During the course, a simple alkaline mixture, containing sodium bicarbonate, 60 grammes, given three times a day, assists absorption.

Course.—Commencing at 07·00 hours daily.

1st day: Initial dose of 4 tablets (2 grammes), followed by a dose of 2 tablets (1 gramme) every two hours for five doses.
2 tablets (1 gramme) at midnight.

2nd and 3rd days: 2 tablets every two hours for six doses.
2 tablets at midnight each night.

4th day: 2 tablets every three hours for five doses.
2 tablets at midnight.

Total for the course = 56 tablets (28 grammes).

If necessary, the course may be repeated after a rest interval of three days.

Sulphonamide.—It is essential to wait for at least ten days before commencing treatment. Patients are kept in bed during this period and warned against the infectivity of their disease, especially as regards conjunctival infection. If the urethral discharge is scanty and the disease mild, a bottle of beer a day is given. The complement-deviation test is done soon after admission and again in a week's time. Total white blood-count is also made early and repeated in three to four days.

If the complement-deviation test becomes positive or if complications, such as acute epididymitis or acute prostatitis, supervene, drug treatment can be commenced immediately, otherwise the full ten days' wait is insisted on.

During the preliminary period, subcurative doses (half or quarter normal) of vaccine are an advantage, but should be discontinued if any general reaction follows.

The course given is exactly the same as that described in detail under M & B 693, above.

No local treatment is necessary in a straightforward case treated with either M & B 693 or sulphonamide, but only in those cases which are resistant to the drug.

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STATISTICS.

OBSERVATIONS ON A FURTHER 93 CASES TREATED. ALL FIGURES ARE AVERAGE.

Method number 1	Number of cases 2	Drug used 3	Amount of drug per diem 4	Total amount of drug per case 5	Preliminary treatment 6	Day of disease on which the drug was commenced 7	Number of days required to effect cure from the date of commencing the drug 8	Total number of days under treatment from the date of onset 9	Number of cases which relapsed subsequently 10	Remarks 11
			grms.	grms.						
16	13	Sulphanilamide	6	24	Nil	14	8	22	1*	*The cases which relapsed, reacted to a further course later
17	17	Sulphanilamide	6	24	Vaccine (full doses)	16	12	28	1*	†Two of the cases in this series were resistant (one of them suffered from thyroid deficiency and it is interesting to note that he had previously been resistant to antisyphilitic treatment for the past three years). These cases were later given M & B 693 and eventually responded to prolonged local treatment.
18	8	Sulphanilamide	7	28	Vaccine (full doses)	10	11	21	1*	
19	11	Sulphanilamide	7	28	Vaccine (full doses)	11	15	26†	—	
20	8	Sulphanilamide	7	28	Vaccine sub-curative doses	13	7	20	—	
21	2	Albucid	7	28	Nil	7	—	—‡	—	‡These cases did not respond and later reacted to M & B 693 therapy.
22	4	Streptocide (oral)	4	24	Nil	7	—	—§	—	§This drug did not appear to be very therapeutically active. In five cases, gonococci were present in smears on the fourth day and in the other two on the 13th and 17th respectively. Four subsequently cleared up under local treatment and three after a course of M & B 693.
23	3	Streptocide (oral and parenteral)	4 10 c.c.	13 30 c.c.	Nil	4	—	—§	—	
24	6	M & B 693	3	24	Nil	5	14	19	—	
25	8	M & B 693	7	28	Nil	10	10	20	—	
26	13	M & B 693	7	28	Nil	5	5	10	—	

All cases were amongst British troops. Indian troops tolerate similar doses equally well.

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