SULPHONAMIDES IN BACILLARY DYSENTERY

FURTHER OBSERVATIONS ON THEIR EFFECTS

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THE results of observations, made at a large desert general hospital in the Middle East (ME) during the 1943 dysentery season, on the relative efficacy of sulphanilamide, sulphapyridine, and sulphaguanidine in bacillary dysentery have previously been reported (Scadding 1944). It was found that groups of patients treated with these three drugs showed no significant difference in duration of diarrhœa or of stay in hospital. The present paper records the continuation of investigations of sulphonamide treatment in bacillary dysentery during the 1944 season at the same hospital.

Because sulphaguanidine is the standard drug for the treatment of bacillary dysentery in ME, and because it is generally believed that sulphonamides have a specific beneficial effect in this disease, only comparative studies, continuing those carried out in 1943, were made during the earlier part of the season. First, succinyl-sulphathiazole and then sulphadiazine were tested against sulphaguanidine. Next, observations without controls were made on the effect of smaller doses of sulphadiazine. Finally, for reasons set out below, it was considered justifiable to carry out a study, scientifically necessary, of strictly alternated sulphaguanidine-treated and control cases. The results will be presented in the chronological order in which the observations were made, illogical though it be.

MATERIAL AND METHOD

The type of dysentery was similar to that of the previous season. It was mild, as shown by the control untreated cases reported below. No acute fulminating case was seen. During each investigation all patients admitted to the dysentery wards with a history of less than five days' diarrhœa and with blood and mucus and a dysenteric exudate in the stools were included in the observed series. The exudate was bacillary—i.e., containing more than 50% of polymorphonuclear neutrophils—in 75–80% of cases in all series and indefinite—i.e., containing less than 50% of polymorphonuclear neutrophils—in the rest. Facilities for culture were not available until the final control series; the results of stool-culture in 99 cases in this series are shown in table IV.

Records were kept by which it was hoped to estimate the relative severity of the illness, and the response to treatment. They are summarised in the tables. The criteria adopted to estimate *severity* were (1) the duration of diarrhœa before admission, (2) the number of stools in the 24 hr before admission, and (3) the incidence of fever. As the highest fever was generally present on admission, it may be included among the criteria of severity. The tables show that the severity of the disease, so estimated, remained almost constant throughout the season. The slightly lower incidence of fever towards the end of the season (table III and the last column of table II) may be related to the end of the very hot weather.

Results of treatment were judged by (1) the duration of fever after admission in febrile cases, (2) the duration of diarrhœa, indicated by the day on which a formed stool was first observed, and (3) the total number of days spent in hospital. Patients were not discharged until they had passed three formed stools free from blood and mucus. In computing for the tables the mean duration of stay in hospital, a few cases in which it was prolonged because of some unrelated disease were omitted. Diarrhœa sometimes recurred during convalescence; the incidence in each series is recorded in the tables.

Treatment, besides sulphonamides, consisted of rest in bed, ample liquid intake, and a bland diet increasing as the patient improved. Sulphaguanidine when used was given in a suspension of 3·5 g. to 1 oz. of water in doses of 7·0 g. followed by 3·5 g. four-hourly, reduced after 48 hr if the patient's condition had improved. The dosage and form in which the other drugs were given are noted below. The average total dose and duration of administration of each drug are recorded in the tables.

No complication, renal, gastric, exanthematous, or other, of sulphonamide treatment developed throughout the investigation.

COMPARISON OF RESULTS WITH SUCCINYL-SULPHATHIAZOLE AND WITH SULPHAGUANIDINE

Succinyl-sulphathiazole is even less well absorbed than sulphaguanidine, only 5% of a dose given by mouth being excreted by the kidneys; it remains within the lumen of the bowel and is active there, in normal conditions, against coliform organisms (Poth et al. 1942). Hence, on the hypothesis which led originally to the introduction of sulphaguanidine for the treatment of dysentery—i.e., that a sulphonamide which is retained in high concentration in the bowel contents is likely to be effective—succinyl-sulphathiazole would be expected to be better than sulphaguanidine.

In June and July, 1944, alternate members of a series of 100 consecutive patients with bacillary dysentery were treated with sulphaguanidine, and the rest with succinyl-sulphathiazole. The latter drug was given in suspension in water in doses of 2 g. five times daily for 3 days, then four times daily for 4 days, the course being cut short if there was early improvement. The results are recorded in table I, which shows that the cases in the two groups were of similar severity; that the durations of fever and of diarrhœa were very similar; and that the only difference is that the sulphaguanidine-treated patients were in hospital, on the average, 1·3 days longer than those treated with succinyl-sulphathiazole, and showed a greater tendency to recurrence of diarrhœa during convalescence.

COMPARISON OF RESULTS WITH SULPHADIAZINE AND WITH SULPHAGUANIDINE

Sulphadiazine presents a complete contrast to succinyl-sulphathiazole in being readily absorbed. Hardy and Watt (1944a) state that bacillary dysentery responds earlier to sulphadiazine and other well-absorbed sulphonamides than to poorly absorbed sulphonamides.

In August and September, 1944, alternate members of a series of 100 consecutive patients were treated with sulphaguanidine, and the rest with sulphadiazine. The latter drug was given in 0·5 g. tablets in doses of 1·0 g. five times daily, reduced after 48 hr, if there was improvement, to thrice daily. The results are recorded in table II, which shows that the cases in the two groups are comparable in severity. Those treated with sulphadiazine had, on the average, slightly shorter fever and very slightly shorter duration of diarrhœa and of stay in hospital.

OBSERVATIONS ON TREATMENT WITH SMALLER DOSES OF SULPHADIAZINE WITHOUT CONTROLS

In September and October, 1944, the effect of reducing the dosage of sulphadiazine was observed without controls. At first 4 g. daily and then 3 g. daily was given. The results were very little different from those obtained with 5 g. daily; those obtained in 57 cases treated with 3 g. daily (average dose 11·4 g. in 4 days) are recorded in table II, which shows that, comparing this group with the others summarised in the same table, though the series was not directly controlled, the severity of the cases was similar, except that the incidence of fever was slightly less, the fever and the diarrhœa very slightly longer, and the stay in hospital rather shorter than in the series treated with larger doses.

CONCURRENT SERIES OF SULPHAGUANIDINE-TREATED AND CONTROL UNTREATED CASES

In discussing the 1943 observations at this hospital, I remarked that a possible conclusion was that, in the mild type of dysentery treated, none of the three drugs—i.e., sulphanilamide, sulphapyridine, and sulphaguanidine—had any specific effect, though clinical impressions and the published experience of others were against this view (Scadding 1944). The uniformity of the course of the disease in both the present and the 1943 series of investigations, in cases receiving varying dosages and various sulphonamides, both readily and poorly absorbable, brought this opinion very forcibly to mind, and made it clearly necessary to test the hypothesis that, under the conditions of the investigation and by the criteria adopted, no effect of the sulphonamides tested on the clinical course of the type of dysentery treated was detectable.

Accordingly a series of strictly alternated sulphaguanidine-treated and control cases was arranged. The controls received a suspension of gr. 20 (1·3 g.) of calcium carbonate to the ounce, which was given in the same volume-dosage and frequency as the suspension of sulphaguanidine. This control suspension was chosen because it closely resembles one of sulphaguanidine, and because it can reasonably be supposed that such a small dose of such an inert substance can have no appreciable effect on the course of the disease. To avoid the danger of leaving a seriously ill patient untreated with a possibly beneficial drug, advantage was taken of the fact that it had been shown that sulphadiazine is at least as effective as sulphaguanidine, and it was ruled that any patient on either suspension about whom any anxiety was felt should cease taking the suspension and be given sulphadiazine.

Soon after this series was started it became possible to perform routine stool-cultures. These were done in 99 of the 133 cases. During 10 days of the total period the overheating of an incubator seriously reduced the number of isolations ; this affected the results of about a third of the cultures performed. Nevertheless, there were 45 isolations, distributed among the various bacterial types as shown in table IV. The distribution is very similar to that observed in ME in 8665 cases by Fairley and Boyd (1943). It will be noted that the bacterial types are almost evenly distributed between the treated and the control groups.

Table III sets out the results obtained in this strictly controlled series. Further, the figures for the cases in which an organism of the Flexner group was isolated from the stool are set out separately ; there were 17 of these in the treated and 17 in the control group.

The table shows that the cases in the two groups were of comparable severity. The control group of 67 patients had formed stools in a mean time of 5·0 days after admission, remained in hospital for a mean time of 12·3 days, and those who were febrile remained so for a mean time of 2–3 days after admission ; whereas the corresponding figures for 66 patients treated with a mean dose of 72 g. of sulphaguanidine in 4–6 days were 4·4, 10·8, and 1·7 days. One patient in each group was thought to be making such unsatisfactory progress that the suspension was changed to sulphadiazine 1·0 g. four times daily : in both improvement followed, but clearly the significance of this event is doubtful.

The figures for duration of diarrhœa and of stay in hospital have been analysed statistically, with the following results :

(1) *Duration of diarrhœa :*

Treated cases : mean (days) 4·4 ; standard deviation 1·3.
Control cases : mean (days) 5·0 ; standard deviation 2·6.
Difference of means 0·6.
Standard error of difference of means 0·36.

(2) *Duration of stay in hospital :*

Treated cases : mean (days) 10·8 ; standard deviation 6·6.
Control cases : mean (days) 12·3 ; standard deviation 7·7.
Difference of means 1·5.
Standard error of difference of means 1·25.

In both instances the difference of the means, being considerably less than twice its standard error, is not statistically significant.

In the 34 proved Flexner cases the difference between the 17 treated and the 17 controls was even less ; if allowance is made for the fact that the average duration before admission in the treated cases was half a day longer than in the controls, there is nothing to suggest that sulphaguanidine had any influence whatever on the course of the disease ; the mean total duration of diarrhœa from the onset (not from admission) is 7·0 days in both groups, and the total duration from onset to discharge from hospital is 12·5 days in both groups.

An interesting point is that the control suspension, which was given in the same way as the sulphaguanidine suspension, was found to have been administered in almost exactly the same total volume-dosage and for the same period as the sulphaguanidine. For instance, in the Flexner cases the average total dosage of both sulphaguanidine and control suspensions was 21 oz. in 4 days.

It is possible that in the figures for all cases a beneficial effect on a few severe infections was being masked by dilution with a large number of mild self-terminating ones. Consideration of the small number of Shiga cases lends some support to this hypothesis, although obviously no conclusion can be drawn from only 6 cases. The 3 in the control series had formed stools in 12, 11, and 18 days, and were in hospital 21, 30, and 34 days, and the last of these was the one case in the control series which eventually received sulphadiazine ; whereas the 3 in the sulphaguanidine-treated series had formed stools in 5, 7, and 7 days, and remained in hospital 9, 26, and 12 days. But the severity of the control cases on admission was greater ; their average number of stools in 24 hr before admission was 22 and their average temperature on admission 101·4° F, whereas the corresponding figures for the treated cases were 15 and 99·3° F. Thus no definite conclusion can be drawn, especially as very great variations in the severity of Shiga infections have been observed in this area ; though the evidence seems very suggestive that in this type of case the sulphonamides were beneficial. In this connexion it is interesting to note that Gard (1943) regarded a duration of diarrhœa for an average of 11·5 days in 25 sulphaguanidine-treated cases of Shiga dysentery as a good result of treatment.

DISCUSSION

Many favourable reports on the action of sulphonamides in bacillary dysentery have been published, but few with adequate controls. Good results in uncontrolled series of cases treated with sulphaguanidine have been claimed by Marshall et al. (1941), Lyon (1941, 1942), Fairley and Boyd (1942), Brewer (1943), Bulmer and Priest (1943), Gard (1943), and others. Similar results in more or less controlled series have been reported by Anderson and Cruickshank (1941), who used extremely small doses the activity of which may well be doubted, Clay (1943), and Adams and Atwood (1944). Jamieson et al. (1944) found in a series of not as a rule severe infections, 75% with Flexner strains and 20% with Sonne, that stools were normal in 100 patients treated with sulphaguanidine in an average of 5·0 days, in 50 treated with chalk in 6·0 days, and in 50 treated with aperients in 6·5 days.

Succinyl-sulphathiazole has been reported on favourably in uncontrolled observations by Poth et al. (1942), and Lyon (1943). On the other hand, Roberts and Daniels (1943) report an outbreak of mild dysentery due to a Flexner strain in which 89 patients treated with succinyl-sulphathiazole were compared with 136 untreated controls ; no significant difference in degree or duration of diarrhœa or in amelioration of symptoms was noted, though there was a reduction in the convalescent carrier-rate.

The absorbable sulphonamides have been considered efficacious in uncontrolled observations by many workers : for instance, sulphapyridine by Reitler and Marberg (1941), Masefield (1941), Paulley (1942), and Swyer (1943), and sulphathiazole by Ferriman and Mackenzie (1944).

Hardy and Watt (1944a) have studied the effects of three poorly absorbed compounds, sulphaguanidine, succinyl-sulphathiazole, and phthalyl-sulphathiazole, and of five well-absorbed compounds, sulphathiazole, sulphadiazine, sulphamethazine, sulphamerazine, and sulphapyrazine, and state that it was evident, through a comparison with findings in untreated controls, that all these sulphonamides were beneficial in patients with " shigellosis " ; the only two of their publications (Hardy and Watt 1944a and b) to which I have had access do not quote their actual data.

Observers who have reported on Sonne infections agree that these are little, if at all, affected by any sulphonamide except possibly succinyl-sulphathiazole (Hardy and Watt 1944b, Fairbrother 1944, Adams and Atwood 1944).

Scott (1945) has assessed the value of sulphaguanidine treatment in ME by comparing the duration of stay in hospital of patients with bacillary dysentery in 1940 before, and in 1943 after, the use of sulphaguanidine became general. He found that the mean duration of stay in hospital in 1940 was 12·7 days and in 1943 was 11·6 ; the difference is statistically significant, but he considers that the discontinuance of routine purgation is a possible contributory factor in this reduction.

Although the data presented in this paper have no relevance to the efficacy of sulphonamides in controlling the carrier state after bacillary dysentery, it is of interest to note that even on this topic reports are conflicting.

TABLE I—CONCURRENT SERIES OF CASES TREATED WITH SUCCINYL-SULPHATHIAZOLE AND OF CASES TREATED WITH SULPHAGUANIDINE (JUNE–JULY 1944)

TABLE II—CONCURRENT SERIES OF CASES TREATED WITH SULPHADIAZINE 5 G. DAILY AND OF CASES TREATED WITH SULPHAGUANIDINE (AUGUST–SEPTEMBER 1944), AND UNCONTROLLED SERIES TREATED WITH SULPHADIAZINE 3 G. DAILY (SEPTEMBER–OCTOBER, 1944)

TABLE III—CONCURRENT SERIES OF SULPHAGUANIDINE-TREATED AND CONTROL CASES (OCTOBER–NOVEMBER, 1944)

	I		II			III			
			Concurrent		Uncontrolled	All cases		Proved Flexner cases only	
	Succinyl-sulphathiazole*	Sulphaguanidine*	Sulphadiazine (5 g. daily)	Sulphaguanidine	Sulphadiazine (3 g. daily)	Sulphaguanidine	Control	Sulphaguanidine	Control
Total no. of cases ..	50	50	50	50	57	66	67	17	17
Severity									
Mean duration before admission (days) ..	2·1	2·1	2·1	2·3	2·5	2·8	2·6	3·0	2·5
Mean no. of stools in day before admission ..	13·0	12·7	12·2	11·5	12·2	13	13	13	12
Fever : percentage febrile	80%	86%	80%	84%	65%	58%	61%	65%	59%
Mean maximum recorded in febrile cases ..	99·8° F	100·1° F	100·4° F	100·0° F	100·4° F	100·4° F	100·8° F	100·2° F	101·4° F
Results									
Mean duration of fever in febrile cases (days) ..	1·6	1·7	1·2	1·6	1·4	1·7	2·3	1·6	2·3
Mean duration of diarrhœa after admission (days)	3·5	3·4	3·9	4·3	4·3	4·4	5·0	4·0	4·5
Mean stay in hospital (days)	10·2	11·5	11·6	12·3	10·5	10·8†	12·3†	9·5‡	19·0
Recurrent diarrhœa during convalescence ..	nil	3 cases	1 case	2 cases	1 case	3 cases	nil	1 case	nil
Dosage (grammes)									
Minimum	14	31·5	8	30	5	31·5	..	31·5	..
Maximum	54	143·5	27	112	22	129·5	..	126·0	..
Mean	38	80·5	17·4	69	11·4	72·0	..	74·5	..
Duration of treatment (days)									
Minimum	2	2	2	2	2	3	..	3	..
Maximum	5	8	7	8	7	9	..	7	..
Mean	..	..	4·3	4·5	4·0	4·6	..	4·0	..
Further treatment with sulphadiazine						1 case	1 case	nil	nil

* 4 cases in the succinyl-sulphathiazole and 1 in the sulphaguanidine series in which the stay in hospital was extended because of another disease were omitted in calculating these figures.

† In computing these figures, 1 patient in the treated and 2 in the control group whose stay in hospital was prolonged because of unrelated conditions are omitted.

‡ In computing this figure, 1 patient who remained in hospital for 40 days because of recurrent diarrhœa is omitted, as it introduces a large bias into such a small series. If this case is included, the figure for mean stay in hospital for treated Flexner cases increases to 11·4.

Hoagland et al. (1943) report uniformly good results in the treatment of carriers of *Shigella paradysenteriæ* (Flexner and allied strains) with sulphaguanidine and succinyl-sulphathiazole ; Barker (1943) had some difficulty in controlling Flexner carriers with succinyl-sulphathiazole ; Fairbrother (1944) speaks with some reserve of the results of attempts to clear carriers of dysentery bacilli with sulphaguanidine if stringent tests of clearance are applied ; while Sandweiss (1944), comparing 33 carriers treated with phthalyl-sulphathiazole with 39 untreated carriers, states that the drug did not appear to influence the carrier state, and that in fact a higher proportion of his treated cases continued as carriers.

Thus, there is still no agreement about the value of sulphonamides in dysentery. And the interpretation of the data here presented is difficult. The following statements seem permissible :

(1) In a mixed group of dysenteries, presumably due to several strains of bacilli, sulphaguanidine-treated cases showed a slight advantage over controls in mean duration of diarrhœa and of stay in hospital, but the differences were not statistically significant. It may be that an effect on a few more severe cases was being masked by dilution with a large number of mild self-terminating cases, because (*a*) in a group of 34 mild Flexner infections, equally divided between the treated and control series, no clinical effect of sulphaguanidine could be demonstrated ; and (*b*) in 6 Shiga infections there was very suggestive evidence that sulphaguanidine and sulphadiazine were beneficial, though the small number of cases observed permits no definite conclusion.

TABLE IV—BACILLARY TYPES ISOLATED IN 99 CASES OF THE SERIES SUMMARISED IN TABLE III

—	Total	Sulphaguanidine-treated	Control
No. of cases in which stools were cultured	99	44	45
Isolations			
Total	45	22	23
Flexner	34 (75·6%)	17	17
Shiga	6 (13·3%)	3	3
Para-shiga ..	1 (2·2%)	..	1
Sonne	2 (4·4%)	2	..
Schmitz	2 (4·4%)	..	2

The figures in parentheses indicate the percentages of the total isolations constituted by each bacterial type.

(2) In a similar mixed group of dysenteries comparative observations between sulphaguanidine and succinyl-sulphathiazole, and between sulphaguanidine and sulphadiazine, showed differences in mean duration of fever, of diarrhœa, and of stay in hospital smaller than those between the sulphaguanidine-treated and untreated control groups. Such as they are, they favour sulphadiazine, and to a less extent succinyl-sulphathiazole, over sulphaguanidine ; and this applies even when dosage of sulphadiazine is reduced to 3 g. daily.

A difference of the same order in favour of two soluble sulphonamides, sulphapyridine and sulphanilamide, was found in the 1943 observations (Scadding 1944). Though the evidence presented is not conclusively in favour of any sulphonamide, it favours, if any, the readily absorbable more than the poorly absorbable ones.

SULPHADIAZINE IN CHRONIC BACILLARY DYSENTERY

Where statistical evidence is so equivocal, it is perhaps permissible, even though dangerous, to mention clinical impressions. I have been impressed by a number of cases in which sulphadiazine has seemed to cut short a long-continued bacillary-type dysentery on which the poorly absorbed sulphonamides had had no effect. The following brief case-records illustrate this point.

CASE 1.—A man, aged 44, was admitted with a history of intermittent diarrhœa with blood and mucus for 2 months. Microscopy of the stool showed bacillary exudate ; from a culture at a later date no pathogens were isolated ; many examinations were negative for *Entamœba histolytica*. He received a course of 150 g. of sulphaguanidine in 8 days without effect ; 23 days after admission he was still passing 3 stools daily with blood and mucus.

Sigmoidoscopy showed gross thickening and redness of the mucosa, with many submucous hæmorrhages, and much mucopus. He then received 62 g. of succinyl-suphathiazole in 7 days ; no definite benefit followed this, and 55 days after admission a second sigmoidoscopy showed no appreciable change in the appearances. He was then given sulphadiazine 5 g. daily for 7 days. Immediate improvement followed ; the stools were reduced to 1 or 2 daily, usually with mucus. Sigmoidoscopy 80 days after admission showed only slight thickening and hyperæmia of the mucosa. He was discharged to convalescent depot 86 days after admission, the stools then being normal, once daily, with only occasionally a little mucus. The condition has subsequently relapsed and once more responded to sulphadiazine.

CASE 2.—An officer, aged 29, was admitted with a history of 14 days' diarrhœa, 5–6 times daily, with blood and mucus. Sulphaguanidine given in the usual doses for 4 days had no effect. *Sigmoidoscopy* after this showed general thickening and redness of the mucosa up to 3 in., but above this was normal. He was still passing loose stools with some blood and mucus 26 days after admission, and an indefinite exudate was found microscopically. From the 27th to 35th day he received sulphadiazine 5 g. daily ; after the second day of this treatment the stools became normal and remained so until he was discharged fit on the 43rd day after admission.

In the following case a patient with bacillary dysentery developed arthritis while receiving sulphaguanidine, and both the dysentery and the arthritis responded well to sulphadiazine.

CASE 3.—A man, aged 23, was admitted with a history of 3 days' diarrhœa with blood and mucus ; 25 stools in 24 hr before admission. Microscopy of the stool showed indefinite exudate. Sulphaguanidine was started in the usual doses. On the 3rd day of treatment with sulphaguanidine the right knee became swollen and painful, and temperature rose to 100° F. On the following day the other knee was swollen, temperature 100·6° F, and 10 stools with blood and mucus had been passed in 24 hr in spite of continued sulphaguanidine treatment. This was stopped after 73 g. had been given, and sulphadiazine 5 g. daily was substituted. Improvement followed immediately. The next day the temperature was normal, the stools steadily diminished in number until on the 4th day of sulphadiazine treatment they were normal, and the arthritis rapidly subsided. He received 30 g. of sulphadiazine in all and was discharged fit 21 days after admission.

It is a plausible hypothesis that in these chronic cases the mode of action of sulphonamides is to combat invasion of the bowel wall by secondary invaders, by virtue of their concentration in the blood, rather than on the dysentery bacilli by their concentration in the lumen of the bowel, where there are likely to be inhibitory substances ; certainly in severe cases there is an inhibitory substance—i.e., pus—in the lumen of the bowel. If this be true, it explains the superiority of the soluble sulphonamides. Also, on the hypothesis that the mode of action of sulphonamides in acute cases is simply prophylactic against ulceration, either by the action of the dysentery organisms or by secondary invaders, it is easy to explain (1) the difficulty of detecting any effect in groups of mild cases, in which no ulceration is likely to develop in any event, (2) the irregular response in severe cases, since response will depend on what secondary invaders are prominent in any given case, and (3) the fact that small doses of readily absorbable sulphonamides, which for other infections would be regarded as prophylactic rather than therapeutic, give as good results in acute bacillary dysentery as larger ones, and possibly better results than very much larger doses of the poorly absorbable compounds.

Estimations of the sulphonamide content of the blood were not possible in the reported series, but it seems likely that the blood sulphonamide content produced by giving 21 g. daily of sulphaguanidine, of which it is known that over 50% may be excreted in the urine, is not very different from that produced by the small doses (3–5 g. daily) of sulphadiazine. On the hypothesis advanced above it would be expected that penicillin parenterally would be as effective as or more effective than either poorly or well absorbed sulphonamides in bacillary dysentery. A trial of penicillin, especially in severe cases, seems well worth while ; though, as has been shown, the simplest of treatment suffices for the ordinary mild case.

CONCLUSIONS

The only definite conclusions that can be drawn from these and my previous observations (Scadding 1944) is that the absorbable sulphonamides, even in small doses, were at least as effective as, and possibly more effective than, the poorly absorbable sulphonamides in the treatment of bacillary dysentery of the type at present seen in ME. On the question of the effectiveness of the sulphonamides in general, no statistically satisfactory evidence was obtained, though the clinical impression that severe and some chronic cases benefited, especially from moderate doses of sulphadiazine, was strong. The observations were relevant only to the therapy of the individual case ; the important question of the effect of sulphonamides on the carrier state was not investigated.

SUMMARY

The therapeutic effects of sulphaguanidine, succinyl-sulphathiazole, and sulphadiazine have been investigated in observations on 390 unselected cases of acute bacillary dysentery.

The disease was on the whole of a mild type. A series of 67 control cases were treated by rest and diet only, except 1 with a Shiga infection whose progress was so poor that sulphadiazine was given. The mean duration of diarrhœa in this group was 5·0 days and of stay in hospital 12·3 days. The corresponding figures for 66 alternate cases treated with sulphaguanidine were 4·4 and 10·8 days ; and in this group also 1 case made such slow progress that additional treatment with sulphadiazine was given. The differences between treated and untreated groups are not statistically significant.

Of 34 Flexner cases 17 were in the sulphaguanidine-treated and 17 in the control group ; there was no difference in the course of the disease in the two groups.

In 6 Shiga cases there was suggestive evidence that sulphonamide treatment had proved beneficial.

In comparative studies of succinyl-sulphathiazole and sulphaguanidine, and of sulphadiazine and sulphaguanidine, the differences in results were small ; sulphadiazine, even in doses as small as 3 g. daily, gave results very slightly better than those given by sulphaguanidine.

Good results are reported in the treatment of a few cases of chronic bacillary dysentery with sulphadiazine.

A hypothesis is advanced to account for the observation that prophylactic doses of absorbable sulphonamides are at least as effective as large doses of either readily or poorly absorbable sulphonamides.

ADDENDUM

Since this paper was written a United States War Department Technical Bulletin (1944) has come to hand, recommending sulphadiazine in doses of 2 g. initially, followed by 1 g. four times a day, as the drug of choice in the treatment of bacillary dysentery.

I am indebted to the sisters and medical officers at various times in charge of the dysentery wards for their coöperation, without which this work could not have been done; to Major L. G. Cook for the stool cultures; and to Lieut.-Colonel R. B. Scott for help with the statistical analysis.

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EFFECTS OF ARTIFICIAL DEHYDRATION IN RHEUMATISM

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THE clinical effect of altering the volume and distribution of the body fluids has been studied at a general hospital in cases of fibrositis, acute and subacute articular rheumatism, and sciatica.

FIBROSITIS

It is now generally accepted that the pain in true fibrositis is associated with circumscribed areas of local tenderness usually called trigger points, and that the symptoms can often be relieved, sometimes permanently, by injection of procaine into those areas.

These trigger points may be palpable as small tender nodules, especially where they can be compressed against bone. Painless nodules in these regions, however, do not seem to signify rheumatism. In a recent examination of 500 soldiers non-tender nodules were found equally frequently in fibrositic and non-fibrositic subjects, but tender nodules and trigger points were found in only 3% of men who did not give a clear history of fibrositis as compared with 30% in those who did.

Stockman (1920) believed these tender nodules to be foci of inflammatory reaction situated in the deep fibrous tissues or in the muscles (fibromyositis). Elliott (1944) has demonstrated areas of local muscle spasm in various conditions associated with deep pain and tenderness, and has suggested that the pain in fibrositis as well as the trigger points can be explained on this basis. Although we consider that muscle spasm can contribute to the pain and tenderness, we regard it as being a reflex response to irritation from a pathological process situated in tissues outside the muscles.

It has been shown that trigger points occur with great regularity in certain regions of the body, and that these regions coincide with the distribution of basic fatty tissue which persists even in emaciated bodies (Copeman and Ackerman 1944). In the lumbar region pads of fatty tissue overlie the lateral borders of the paravertebral muscles and may be 2 in. thick. This is a common situation for trigger points, and location of these by needling has shown that they are too superficial to be lying in the muscles. In the upper back and shoulders the layer of fatty tissue is thinner, and tender nodules can often be picked up with the subcutaneous tissues between the examiner's finger and thumb. Dissection of these areas of fatty tissue shows that they consist of lobules of fat lying within definite compartments with tough fibrous walls. The lobules do not appear normally to fill the space available within the compartments.

We believe that in fibrositis an important factor in the production of pain and local tenderness is œdema in certain lobules and the development of tension as they swell and fill their compartments. This increase in size may lead to herniation if the fascial walls are partially deficient. In 20 cases of established fibrositis such fat-herniæ were demonstrated at biopsy, and their removal was followed by persistent relief of symptoms. On microscopical examination of the biopsy material no histological evidence of inflammation was found in the form of cellular infiltration, although macroscopically there was obvious œdema and congestion; therefore the swelling must have resulted from some process other than the classical inflammatory reaction.

We thought that we might be able to reverse this process by reduction of the fluid-content of the affected tissues, probably by inducing the clinical state of dehydration. This study was chiefly concerned with cases of fibrositis of the back and shoulders, but many other cases were seen in which other parts of the body were affected. These latter cases showed the same tendency to recurrence and exacerbation in response to infection and climatic influences, and trigger points were found in constant situations corresponding to the distribution of fibro-fatty tissue round tendon sheaths, bursæ, and muscle insertions. It seemed therefore that a similar process of œdema and tension affecting fibro-fatty tissue might be responsible for the symptoms in this type of case also; accordingly they are included separately as chronic rheumatism in the accompanying table.

ACUTE AND SUBACUTE ARTICULAR RHEUMATISM

Most cases of acute rheumatism were of a benign type and of comparatively short duration. In some cases, however, articular pains started to recur in wet weather; whereas others merged into a condition clinically indistinguishable from chronic fibrositis. We repeatedly observed that the articular pain in acute and subacute rheumatism was referred from one or more trigger points near the joint and was not caused, as is generally assumed, by distension of the joint through effusion, which often only happens later in the disease. This can be confirmed by infiltrating these trigger points with procaine, which immediately relieves the so-called articular pain without affecting the effusion. Moreover, tense swollen joints are seen in painless conditions such as hydarthrosis and synovitis.

These observations show that the distinction between acute and subacute rheumatism and fibrositis is not so precise as is generally held, there being many points of resemblance between them. In view of these facts some cases of acute and of subacute articular rheumatism were also submitted to dehydration.

SCIATICA

In planning this experiment it was thought that cases of sciatica due to a prolapse of an intervertebral disk might prove suitable for a control series. The effect of dehydration was therefore tried on several cases, and it was found that, contrary to expectation, they tended to respond to the procedure in a characteristic manner, different from that seen in fibrositis.

FATTY TISSUE AND WATER METABOLISM

The fatty tissues have long been known to be connected in some way with the normal water storage of the body, although not much information appears yet to be available on this subject, except as it affects the hump of the camel.

Chiari (1910) has said that adipose tissue constitutes 18% of the weight of normal persons and is subject to many physiological and pathological variations, although