is to be ascribed to a tendency for the time of conception of children to vary at different levels of parental intelligence.

Moreover, there is little doubt that the difference in fertility has been underestimated. The number of living full sibs was ascertained at a time when many of the families were incomplete. Evidence has previously been presented (Roberts, 1939) to show that, when allowance is made for this circumstance, fertility differences are considerably increased.

Taking the evidence as a whole, the results can be said to be significantly against the hypothesis that season of conception influences intelligence, and therefore in favour of the alternative explanation—that intelligence influences season of conception.

Summary

It is a fact beyond reasonable doubt that children conceived in winter are, on the average, somewhat more intelligent than those conceived in summer. The fact has been almost universally misinterpreted. Practically every hypothesis depends upon the assumption that it is season of conception which influences intelligence, and it has often been urged that planned winter conception would be beneficial. It is shown that if winter children are compared with their summer brothers and sisters the difference vanishes. It is also shown that while winter children differ from summer children in intelligence, they differ even more in having fewer sibs. Thus the observed association is to be ascribed not to seasonal influences on the mother or the developing child, but to a tendency for the children of more intelligent parents to be conceived slightly more often in winter, those of less intelligent parents slightly more often in summer.

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BACILLARY DYSENTERY IN DUNDEE A COMPARATIVE STUDY OF TREATMENTS

BY

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The treatment of bacillary dysentery by sulphaguanidine has opened new fields of investigation. Much of the recent work on this subject has dealt mainly with clinical recovery, but correlation thereof with bacteriological clearance of the stools has received less attention. In this paper are set forth the clinical and bacteriological results obtained in 200 confirmed cases of bacillary dysentery which occurred in Dundee.

Prior to 1941 the criterion for discharge of cases of dysentery from King's Cross (Infectious Diseases) Hospital, Dundee, was purely clinical—i.e., the reversion to normal stools for a period of approximately four days. Late in 1941 examination of faeces in convalescence was undertaken to determine the "convalescent" carrier rate and so find out whether the discharge of patients on clinical evidence alone was possibly contributing to the maintenance of the infection in the community.

The investigation, begun in this way, was extended to a study of the effects of different methods of treatment not only on the course of the disease but also on the incidence of the carrier state in convalescence. The first specimen of faeces in convalescence, irrespective of the treatment adopted, was examined four to six days after the disease had subsided clinically—i.e., at the time when by former standards the

patient would have been discharged from hospital. Thereafter faeces were examined twice weekly until three consecutive negative results were obtained.

The gross figures for bacillary dysentery from 1937 to Aug. 31, 1943, are set forth in Table I.

TABLE I

Year	Notifications	No. Admitted to Hospital	No. Accepted Clinically	No. Confirmed Bacteriologically	Clinical Cases Confirmed Bacteriologically (%)
1937	47	50	23	13	57
1938	325	271	141	45	32
1939	172	169	96	40	42
1940	390	279	183	78	43
1941	420	275	153	73	48
1942	421	322	213	148	69
1943 (8 mths.)	173	130	91	65	71

The table shows that, with the exception of 1939, there was a steady, if slight, increase in the number of notifications. There was also a steady rise in the percentage of clinically accepted cases confirmed bacteriologically since 1938. In 1937 the numbers were so small that comparison with 1938–43 cannot be made. This steady rise can be ascribed to improvements in laboratory technique. For about 15 years prior to 1939 faeces were collected in outfits containing Teague's fluid (Teague and Clurman, 1916) and plated direct on neutral red agar (MacConkey, 1908). In 1939 Sachs's (1939) modification of Teague's fluid was adopted and MacConkey's agar was modified in that the nutrient basis became serum-peptic-digest-lemco broth (Brodie, 1942). Towards the end of 1941 a selective solid medium and a fluid enrichment broth for the isolation of *B. dysenteriae* and pathogenic members of the colon-typhoid group were elaborated. These consisted of serum-peptic-digest-lemco-bile-salt-iron-citrate-rosolic-acid-lactose (C.R.A.) agar and the corresponding C.R.A. broth (Brodie, 1942). The fluid medium has since been modified by the omission of the lactose, but the sugar must not be omitted from the solid medium.

It will be seen that the percentage of bacteriologically confirmed cases rose with these various improvements in laboratory technique. The present investigation covers the whole of 1942 and 1943 up to Aug. 31, and during this period the media employed for isolation were C.R.A. agar and C.R.A. broth.

Methods of Treatment

The series comprised a total of 200 cases, all confirmed both clinically and bacteriologically. Three types of treatment were adopted, as follows:

(a) *Aperients* (50 Cases).—An initial dose of ol. ricini was given, followed by thrice-daily doses of milk of magnesia for children and of sodium sulphate for adults, the dosage being reduced as abnormal constituents disappeared from the stools.

(b) *Sulphaguanidine* (100 Cases).—At first the dosage used was small, being in accordance with that suggested by Anderson and Cruickshank (1941); but both clinical and bacteriological results were disappointing, as no fewer than 12 out of 15 cases so treated yielded positive cultures in convalescence. All 15 cases were infections due to *B. dysenteriae* (Flexner). No further reference is made to these cases. In consequence of this result and because larger doses were advocated by Marshall *et al.* (1941), increased dosage, based for convenience on age instead of body weight, was instituted (Table II). The tablets were crushed and given in water, the daily dose being divided into four equal six-hourly portions. In all, 100 cases were so treated, and no toxic effects from the drugs were observed.

TABLE II.—*Dosage of Sulphaguanidine*

Age in Years	Grammes per Day					Total in Grammes
	1st	2nd	3rd	4th	5th	
0–2	6	2	2	2	2	14
2–5	10	4	4	4	4	26
5–12	20	6	6	6	6	44
Over 12 ..	30	8	8	8	8	62

(c) *Chalk Mixture* (50 Cases).—Large doses of sulphaguanidine have a constipating action. It was decided, therefore, to employ in the third group a simple remedy—namely, chalk—which would produce a similar effect without exerting the inhibitory qualities on the dysentery bacillus claimed for sulphaguanidine. The amount

of chalk administered for each age group was twice the weight of sulphaguanidine shown in Table II. On several occasions this treatment was supplemented by the oral administration of tinct. opii.

In all groups abundant fluid was given orally, and parenterally when required. There were no special dietary restrictions.

Clinical Features

Most of the cases occurred in children under the age of 10 years—only 25%, approximately, being over that age. Pyrexia was not a notable feature, and when present it usually subsided within 48 hours of the beginning of treatment. The clinical appearance of the stools varied between loose offensive motions and the typical "pus-blood-and-mucus" dysentery stool. The clinical features are summarized in Table III. No fatal case was encountered in the series.

TABLE III

Type of Treatment	No. of Cases	No. with Pyrexia		Appearance of Stools		
		98-4° F. to 100° F.	Over 100° F.	Blood and Mucus	Mucus	Loose
Aperients	50	11	9	17	30	3
Sulphaguanidine	100	15	15	44	49	7
Chalk	50	11	7	33	14	3

Clinical Results of Treatment

Disappearance of mucus from the stool with return to normal consistency was regarded as "clinical cure." The average duration of symptoms after admission is shown in Table IV, the cases being subdivided according to method of treatment and type of infecting organism.

TABLE IV

Type of Treatment		Type of Organism				All Types
		Flexner	New-castle	Sonne III	Mixed	
Aperients	No. of cases	16	21	11	2	50
	Av. dur. symptoms (days)	6.4	7.0	6.3	4.5	6.5
Sulphaguanidine	No. of cases	51	34	10	5	100
	Av. dur. symptoms (days)	4.8	4.9	4.7	8.0	5.0
Chalk	No. of cases	6	23	18	3	50
	Av. dur. symptoms (days)	4.0	5.3	7.6	6.3	6.0

So far as "clinical cure" was concerned, sulphaguanidine treatment yielded better results than did aperients. In the chalk series duration of symptoms in Flexner and Newcastle infections approximated to the corresponding subdivisions in the sulphaguanidine group, whereas with Sonne III infections sulphaguanidine seemed to give better results. Furthermore, in the sulphaguanidine group the type of infecting organism did not materially alter the duration of symptoms. The mixed infections in each treatment group were too few to allow of comparison.

The incidence of relapse in each group was fairly constant, there being 5 instances in the aperient series, 10 in the sulphaguanidine, and 4 in those treated with chalk.

Bacteriological Results of Treatment

The bacteriological findings in convalescence are shown in Table V. In this table "negative" means that in convalescence no dysentery bacilli were isolated, while the term "positive" indicates that micro-organisms were recovered from one or more specimens.

TABLE V.—Bacteriological Findings in Convalescence

Type of Treatment		Type of Organism				All Types
		Flexner	New-castle	Sonne III	Mixed	
Aperients	No. of cases negative	8	10	7	0	25
	% pos. after treatment	8	11	4	2	25
Sulphaguanidine	No. of cases negative	50	52.4	36.4	100	50
	% pos. after treatment	36	26	6	2	70
Chalk	No. of cases negative	15	8	4	3	30
	% pos. after treatment	29.4	23.5	40	60	30
	No. of cases negative	5	12	7	0	24
	% pos. after treatment	1	11	11	3	26
	No. of cases negative	16.6	47.8	61.1	100	52
	% pos. after treatment					

On the whole the group of cases treated with sulphaguanidine gave better results than did either of the other groups, although treatment of Sonne III infections with aperients was slightly better than with sulphaguanidine. The low percentage of positive cases in convalescence in the chalk-treated Flexner group cannot be considered a fair comparison owing to the small number of such cases in the series.

The isolation of *B. dysenteriae*, using the media herein described, can be obtained either by direct plating on C.R.A. agar or by subculture following enrichment in C.R.A. broth. An analysis of the isolations obtained by plating compared with those obtained only after enrichment is interesting, and is shown in Table VI.

TABLE VI.—Analysis of Isolations

	Aperients	Sulphaguanidine	Chalk	All Types
No. of diagnostic specimens positive by direct plating	33	70	33	136
No. of diagnostic specimens positive after enrichment only	8	21	12	41
No. of convalescent specimens positive by direct plating	29	24	35	88
No. of convalescent specimens positive after enrichment only	11	21	18	50

It will be noted that there is an apparent discrepancy between the number of positive diagnostic specimens and the total number of cases. This is due to the fact that in 23 cases the infecting organism was isolated only during convalescence. These specimens were therefore considered as convalescent specimens.

The results in Table VI show that the employment of the enrichment technique is amply justified and that direct plating, used alone, can yield a false sense of security as regards freedom from infection. Particularly is this so in convalescence, where no less than 36% of the positive results were obtained only by the enrichment method. Moreover, a number of cases included in this investigation would not have been confirmed bacteriologically and a further number would have been discharged prematurely had not the enrichment technique been employed. These are set out in Table VII.

TABLE VII

	Type of Treatment.			Total
	Aperients	Sulphaguanidine	Chalk	
No. of cases with specimens positive at all stages, but by enrichment only	9	18	7	34
No. of cases in convalescence with all positive results obtained only by enrichment	6	11	3	20

It might be thought that laboratory technique would have no great bearing on the management of cases, but, as will be seen in Table VII, the greatest number of convalescent cases which yielded positive results by enrichment alone fell to the sulphaguanidine group. Moreover, Table VI shows that of a total of 45 positive specimens during convalescence in the sulphaguanidine group, 21 would have yielded false negative findings had enrichment not been used.

The convalescent carrier rate in the sulphaguanidine series, then, is lower than in the other two, but the difference would have been even more striking had only direct plating been employed; for without enrichment the percentage of cases positive after sulphaguanidine would have fallen from 30 to 19%, as compared with from 50 to 38% and from 52 to 46% after aperients and chalk respectively. Furthermore, a certain number of cases which were positive in convalescence by direct plating yielded subsequent positive specimens by enrichment only, therefore prolonging their stay in hospital. Because of this, in 19 cases in the sulphaguanidine group an average of 9.9 days per case was added, while in the aperient group 9 cases were similarly delayed for an average of 7.6 days and in the chalk group 9 cases for 5.5 days.

It may be that the explanation of this prolongation of the "convalescent" carrier rate, particularly in the sulphaguanidine

group, is due to the small number of dysentery bacilli in the faeces—small because of the inhibitory action of sulphaguanidine on the micro-organisms. This will have a direct effect on isolation of the micro-organisms, since if their number be small, so will the possibility of isolation by direct plating be small, whereas "enrichment" in C.R.A. broth followed by plating on C.R.A. agar will enhance the chance of their isolation.

In the aperient group the delay was less than in the sulphaguanidine group but greater than in the chalk. Here the bacilli are washed out of the gut mechanically by purgation, but, since no inhibitory effect is present, propagation of the remaining bacilli can continue unimpeded. Under such conditions direct plating should give more satisfactory results, and so "enrichment" could be expected to exercise less effect in delaying the discharge of convalescent cases from hospital.

Since chalk has a purely mechanical action in producing constipation, the organisms are more likely to be present in larger numbers in the gut, and so direct plating might be expected to give the optimum number of isolations, making the enrichment technique less necessary, and therefore less apt to prolong the "convalescent" carrier rate.

Whether or not the above explanations are correct, the results obtained do indicate the necessity for exercising great care in the handling of faeces from convalescent cases, especially where drugs possessed of properties inhibitory to the dysentery bacilli are employed in treatment.

In Vitro Experiments with Sulphaguanidine

Marshall *et al.* (1940) claim that sulphaguanidine *in vitro* possesses inhibitory, bacteriostatic, or bactericidal effects on the micro-organisms of the dysentery group. The optimum temperature for these effects varies from 39° C. to 41° C., and these temperatures are worthy of note, since their occurrence *in vivo* depends upon the clinical severity of the cases. In the 100 cases surveyed only 30 were pyrexial, and of these 4 had a temperature over 39° C. In view of the claims of Marshall *et al.*, these pyrexial cases treated with sulphaguanidine in sufficient quantity to produce saturation of the gut contents should show the maximum benefit from treatment.

The *in vitro* experiments were designedly performed at 37° C. because of the preponderance of apyrexial infections encountered among the cases discussed. Six smooth and recently isolated organisms were employed—namely, *B. typhosus*, *B. paratyphosus* B, *B. dysenteriae* (Shiga), *B. dysenteriae* (Flexner W), *B. sonnei* III, *B. dysenteriae* var. Newcastle. All were grown for 24 hours in 1% peptone water before subculture into media containing sulphaguanidine. Two loopfuls (1/8 in. diameter) of this growth were used in each instance to inoculate agar slopes, semi-solid agars, and broths, all made according to the method of Huntoon (1918), enough sulphaguanidine having been added to the media to ensure saturation at 37° C., and all tubes being incubated at that temperature after addition of the drug and before inoculation. Subcultures were made at intervals of 24, 48, 72, and 96 hours into 1% peptone water. Visible growth was not accepted unless all subcultures were checked by fermentation and serological tests. In no instance was a bactericidal action revealed on the solid medium, although a bacteriostatic effect was obtained with *B. dysenteriae* (Shiga), but subcultures even in this instance yielded good growths. All the other micro-organisms tested were inhibited, but bacteriostasis was not complete or even striking.

In vitro experiments at temperatures higher than 37° C. were not performed, but the possible effect of pyrexia on the course of the illness is indicated in Table VIII.

TABLE VIII.—Pyrexia in Sulphaguanidine Group

Bacteriological Findings in Convalescence	Normal Temp.	Degree of Pyrexia		
		Normal to 38° C.	38° C. to 39° C.	Over 39° C.
No. of cases negative ..	49	11	7	3
" " positive ..	21	6	2	1
Total ..	70	17	9	4

It would seem, therefore, that the occurrence of pyrexia in sulphaguanidine-treated cases has no marked influence on the bacteriological results in convalescence. It is interesting, however, to contrast the pyrexial with the apyrexial cases in respect of average duration of symptoms following treatment. The average duration in the 30 pyrexial cases was 4.6 days, as compared with 5.2 days for the 70 apyrexial cases. This would suggest that sulphaguanidine is somewhat better in respect of clinical recovery in the more acute type of case. During the period covered by this investigation 5 cases of chronic bacillary dysentery have been treated at varying times with full courses of sulphaguanidine (Table II). In none of these has any improvement in the clinical—or bacteriological—condition been observed following such treatment.

Estimation of Sulphaguanidine

When using sulphaguanidine it is essential to oversaturate the gut contents with the drug. The solubility of sulphaguanidine at body temperature is approximately 200 mg. per 100 c.cm.; therefore the presence of more than this amount can be taken as evidence that saturation has been achieved. Two patients in each age group were investigated as to the amount of free sulphaguanidine in their stools at 24-hour intervals after starting treatment. The method of estimation was that recommended by Bratton and Marshall (1939). The results are shown in Table IX.

As a matter of interest a few urines were also examined for their free sulphaguanidine content per 100 c.cm., and these results are entered in parentheses in their appropriate places in the table. From the figures obtained it is apparent that, despite the claim that sulphaguanidine is not absorbed from the gut to any great extent, an appreciable amount can be demonstrated in the urine.

TABLE IX.—Concentration of Free Sulphaguanidine in Faeces (mg. per 100 g.)

Age Groups (years)		Time of Sampling after starting Treatment				
		24 hrs.	48 hrs.	72 hrs.	96 hrs.	120 hrs.
0-2	Case 1	4,430	456*	1,970	1,450	1,260
	" 2	688*	535*	892	621	876
2-5	" 3	5,450	5,165	6,700	4,274	1,587
	" 4	838	6,180	866*	1,560 (100)	1,493 (93)
5-12	" 5	4,710	6,350	4,388	2,038 (133)	1,877 (154)
	" 6	3,840	8,693	4,740	3,780 (39)	1,255 (58)
Over 12	" 7	13,300	5,430	7,190	4,430	No specimen
	" 8	10,800	3,030	2,850	1,965	1,240

* Fluid stool.

It is evident from the results in Table IX that the dosage adopted, based on age in place of body weight, besides being more practicable, is also quite adequate to oversaturate the gut contents.

Conclusions

The use of sulphaguanidine in bacillary dysentery gives results superior, both clinically and bacteriologically, to those from aperients and chalk, but, even so, 30% of cases are still bacteriologically positive in convalescence, as compared with 50% with the other treatments.

Pyrexia does not appear to influence the effect of sulphaguanidine to any great extent.

The use of the C.R.A. broth-enrichment technique reveals many positive results, particularly in convalescence and in cases treated with sulphaguanidine, which would be missed if direct plating only were employed.

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