x-ray the whole 487 children. Of the five children showing definite tuberculous lesions, one, aged 3 years, came for routine examination; her mother said she had "seemed tired the last few weeks." The V.P.T. was strongly positive, and x rays revealed miliary tuberculosis. She died three weeks later. Another, aged 7, had close contact with his tuberculous father, who died in 1941. The remaining three are Cases 1, 2, and 3, mentioned above.

Housing

The housing of the children is shown in Table III under categories A (good), B (fair), and C (poor). The classification of the houses was made by the public health authorities. In the quinquennium 1921–5 only 41% of St. Andrews children were born in "good" houses; but 628 new houses have been built since that time and a number of old houses reconstructed. It will be noted that, out of the total of 487 children examined, 456 (94%) were well housed at the time of this investigation, and that therefore only 31 (6%) children living in B or C houses were examined with the V.P.T.

TABLE III.—*Housing*

	A	B	C	Total
Negative reactions ..	313	20	3	336
Positive ,, ..	143	7	1	151
Total ..	456	27	4	487

Combining B and C, a fourfold table gives: $\chi^2 = 0.199$; P = 0.66. There is therefore no significant difference between the housing of the two groups.

Morbidity

The mass of data available in each child's record, which is complete from birth, made it difficult to select points in the case history suggestive of tuberculosis. Also, the range of age of the 487 children—from 2 to 16 years—renders any analysis of little value statistically. However, it may be of interest to record that the case histories were examined under the following headings: (i) contact with notified or suspected pulmonary tuberculosis; (ii) respiratory disorders of a degree of at least two attacks of bronchitis or one of pneumonia; (iii) febrile attacks; (iv) operation on cervical glands; (v) poor nutrition; (vi) allergy; (vii) negative to i–vi. The findings are given in Table IV.

TABLE IV.—*Showing Morbidity in 487 Children examined with the V.P.T.*

No. of Cases	i Contact	ii Respiratory	iii Febricula	iv Gland Operations	v Poor Nutrition	vi Allergy	vii Record Neg. for i–vi
V.P.T. neg., 336	50 (15%)	22 (6·5%)	10 (3%)	5 (1·5%)	22 (6·5%)	11 (3%)	233 (69%)
V.P.T. pos., 151	32 (21%)	19 (12·5%)	12 (8%)	5 (3%)	11 (7%)	13 (9%)	81 (54%)

As would be expected, the morbidity is higher in the positive reactors, but it should be noted that 81 (54%) had none of the above signs or symptoms suggestive of tuberculosis. The consensus of opinion is that one cannot differentiate human and bovine infection by tuberculin tests. The fact that five negative reactors had had cervical gland operations strengthens the impression that the V.P.T. does not react so well to bovine infection. Also, one of the children examined was proved bacteriologically to have a bovine infection of lung and kidney, and she was a negative reactor.

Summary

The investigation was undertaken as a specific piece of research on the lines of the original aims of the James Mackenzie Institute "to investigate disease before the occurrence of any structural change in any organ of the body, with a view to providing a diagnosis at a period earlier than is possible by the methods now in use, and in order to obtain a knowledge of the circumstances that favour the onset of disease."

Four hundred and eighty-seven children in a seaside and holiday resort were examined with the Vollmer patch test for tuberculosis, and 31% gave a positive reaction. The children were unselected except for the fact that all had health records from birth. Their housing conditions are tabulated. An analysis is given of the x-ray films of chests in 86% of positive reactors. An attempt has been made to compare morbidity of positive and negative reactors.

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SULPHAGUANIDINE IN THE TREATMENT OF FLEXNER DYSENTERY

BY

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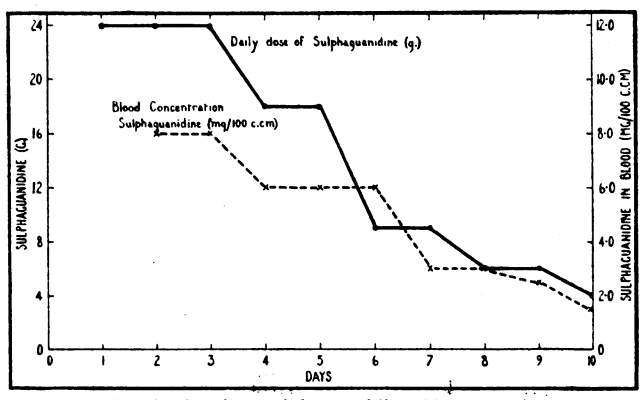
The treatment of dysentery with sulphaguanidine has not gained the measure of approval accredited to the use of the other sulphonamides in many other infections. At least at this hospital the results were not entirely conclusive, although it is true that the majority of cases were of the Sonne type, against which sulphaguanidine is said to be less effective. It should be appreciated that any antibacterial agent is set a severe task when endeavouring to "sterilize" the bowel. The total length of the gut, its further increase in surface area by the throwing up of mucous membrane into folds, together with the dilution of the drug in faecal contents of the bowel, present a major problem in an attack on all parts of the intestine. It was thought that success might follow the administration of relatively large doses of sulphaguanidine, which, by reason of the poor absorption of the drug, would result in a high concentration of the presumed bacteriostatic agent throughout the bowel.

The Investigation

The admission of 44 young female adults, ranging in age from 17 to 37 years (average 21), suffering from Flexner dysentery has given an opportunity of testing the effects of large doses. Unfortunately, when the early admissions were made it was not suspected that such a large number of patients would arrive ultimately, otherwise a controlled observation would have been planned. Certain points, however, make the results worth recording. Of the patients only ten had a record of diarrhoea before admission. The remainder were symptomless contact carriers. Five had received sulphaguanidine before admission, but not more than 10.5 g. During the period in hospital the only clinical manifestations reported were transient blood and mucus in the stools in four and mucous stools in two cases.

Dosage.—The total amount of sulphaguanidine was 142 g., given orally, over 10 days as follows: 24, 24, 24, 18, 18, 9, 9, 6, 6, and 4 g. A number of patients developed a toxic rash (described below), whereupon the drug was stopped; but in no case did any patient receive less than 129 g. in all. The level of sulphaguanidine in the blood was estimated for each day by random selection. Only one specimen of blood was withdrawn from most of the patients, but in some a second estimation



Graph showing sulphaguanidine blood levels.

was made. The first three specimens, taken during the second or third day, were surprisingly high, ranging from 10 to over 14 mg. per 100 c.cm. Accordingly the fluid intake was increased from 4 pints to 6 pints a day. The average blood concentration for each day is represented graphically (see Fig.). It will be seen that the blood concentration follows a pattern essentially similar to that of the daily dose of the drug.

Bacteriological Results.—The bacteriological results obtained at the end of treatment were very satisfactory. Over a period of 14 days three successive rectal swabs and two specimens of faeces from each patient were examined. The stools were non-dysenteric in character, and both faeces and rectal swabs were found to be negative for *B. dysenteriae* (Flexner). In addition, magnesium sulphate was administered to 6 patients to produce watery stools: these gave negative results for *B. dysenteriae* (Flexner).

Toxic Effects.—Previous experience had shown that children tolerate massive doses of sulphaguanidine with no adverse effects. As much as 168 g. of the drug has been given over 16 days, and 330 g. over 28 days, to children aged 2 years. It was surprising, therefore, to find that no fewer than 21 of the 44 adult patients developed a toxic rash between the eighth and tenth days of treatment—mostly on the ninth day. With one exception all the rashes were pink and maculo-papular. Ten were generalized morbilliform rashes (one of which was petechial before fading). In one instance the rash was at first scarlatiniform, but later the same day it became morbilliform in type. The remainder were localized to particular parts of the body, such as the thighs, back, arms, or face. In one case a circinate urticarial rash was recorded. Here, small red macules appeared on the outer aspects of the thighs, spreading out with a pink raised edge to a diameter of about 2 in. and fading in about 24 hours. Three crops occurred before the rash disappeared entirely after 4 days. In other cases the rash faded in from 2 to 3 days. There was little constitutional upset, though a few patients complained of a burning sensation of the face. Two had more severe symptoms, with elevation of temperature to 100° and 101° F., generalized rash, a burning sensation of the skin, swollen face, and pink and suffused eyes.

Longcope (1943) suggests that the following sulphonamide rashes occur in chronological order: (1) urticarial, (2) scarlatiniform, (3) morbilliform, (4) petechial. Hageman and Blake (1937) described ten cases of toxic rash from their series of 134 cases occurring about the seventh and eighth days, and often found a leucocytosis with increase in percentage of eosinophils concomitant with the rash. There was no evidence of a leucocytosis in the present series, though in the majority of cases an increase in the percentage of eosinophils was noted. There was no correlation between concentration of the drug in the blood and the development of a rash. The early blood levels were not higher than the rest of the cases, and at the time the rash appeared the blood levels were usually negligible. No case which developed a rash had received previous treatment with sulphaguanidine.

Sensitization.—In view of the occurrence of such a high percentage of toxic rashes it was decided to obtain information regarding hypersensitivity to the drugs of the sulphonamide series. Accordingly 12 of the 21 cases were divided into 4 groups of 3 individuals, who were given the following single test dose: Group 1, 1 g. sulphanilamide; Group 2, 1 g. sulphathiazole; Group 3, 1 g. sulphadiazine; Group 4, 2 g. sulphaguanidine. No reaction was obtained with the first three drugs. With sulphaguanidine only one patient of the three showed a reaction. A scarlatiniform rash on face and chest made its first appearance one hour after administration, and five hours later became generalized and blotchy. There was no constitutional upset, and in 20 hours the rash had faded. The 9 patients who had previously received the other sulphonamides were later given 2 g. of sulphaguanidine. Seven developed a toxic reaction as follows:

1. Scarlatiniform rash developed on face, neck, and elbows 6 hours after administration. Eyes suffused and painful. Slight elevation of temperature. Faded 12 hours after appearance.

2. Scarlatiniform rash on arms and thighs appeared within 7 hours. Rash faded 12 hours later.

3. Generalized scarlatiniform rash appeared in 7 hours, with suffusion of eyes, photophobia, and sickness. Faded 12 hours later.

4. Generalized scarlatiniform rash appeared in 6 hours. Eyes suffused. No discomfort. Disappeared 11 hours later.

5. Generalized scarlatiniform rash appeared in 6 hours, with severe constitutional symptoms—viz., headache, sickness and vomiting, suffusion of eyes, and elevation of temperature.

6. Generalized scarlatiniform rash appeared in 7 hours. Faded 12 hours after appearance.

7. Scarlatiniform rash on legs appeared in 7 hours. Faded 11 hours after appearance.

Discussion

From the therapeutic point of view the results were very satisfactory. It is unusual to obtain five consecutive negatives from a series of cases of dysenteric infection. On the debit side, however, the occurrence of so many toxic rashes must be regarded seriously, and constitutes a strong argument against massive dosage. It may be suggested that the total dose should not exceed 110 g. in the adult. The results of the investigation of the drug sensitization are considered interesting, and the conclusion drawn is that the primary hypersensitivity encountered was not general for sulphonamides but was confined to sulphaguanidine alone. The evidence seems to suggest that the hypersensitivity was due to the guanidine radical of the sulphonamide compound.

Summary

Forty-four young female adults, mainly symptomless carriers of *B. dysenteriae* (Flexner), were treated with massive doses of sulphaguanidine.

The bacteriological results were satisfactory after conclusion of treatment. Five consecutive negative results were obtained for each patient.

About the ninth day of treatment 21 patients developed a toxic rash. Apart from one circinate urticaria, the rashes were pink and morbilliform. The presence of a scarlatiniform and a petechial type was noted among the latter. There was no relation to a high blood concentration of the drug.

Eight patients out of 12 reacted to a sensitization dose of sulphaguanidine. In some cases the constitutional upset was severe. There was no response to sensitization doses of other sulphonamides. It is suggested that the guanidine radical may be the sensitizing agent.

The high incidence of toxic rashes suggests care in dosage.

I wish to thank Dr. T. Anderson, superintendent of Knightswood Hospital, for constant advice and encouragement throughout this investigation. Thanks are also due to Dr. W. R. Wiseman, Glasgow Public Health Laboratory, who performed the routine bacteriological examinations.

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HAEMOLYTIC DISEASE OF THE NEWBORN

THE PREPONDERANCE OF HOMOZYGOUS Rh-POSITIVE FATHERS

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A predominance of homozygous RhRh fathers in families where an Rh-negative mother has borne children suffering from haemolytic disease of the newborn has been suggested by Race, Taylor, Cappell, and McFarlane (1943). An Rh-negative mother is more liable to be immunized when every pregnancy is Rh-positive and provides the antigenic stimulus, as it does with a homozygous husband, than when he is heterozygous Rhrh and some of the children are positive and others negative. This being so, it is obvious that the proportion of homozygous fathers producing affected children will be greater than the proportion of heterozygous fathers. It can readily be shown that in a random sample of Rh-positive males about 3 out of 7 must be homozygous and 4 must be heterozygous.

Race and Taylor (1943) have described a serum which discloses the genotype of half the persons who are homozygous RhRh. This serum, called "St" from the first two letters of the donor's surname, agglutinates the blood of all Rh-negative rhrh and of all heterozygous Rhrh persons, but it fails to react

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