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.

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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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with about 20% of bloods (St-negative), all of which must therefore be homozygous RhRh and represent about half the Rh-positive homozygotes—about 38% of the population. Race and Taylor pointed out that the extent of any preponderance of homozygotes among the fathers of erythroblastotic children should be indicated by the proportion found to be St-negative. In 46 families in which the disease occurred and in which all the mothers were Rh-negative and had anti-Rh agglutinins in their sera, 18 of the fathers have been St-negative and 28 St-positive. If about half of the homozygotes are St-negative, then it appears that of 46 fathers about 36 were homozygous; these frequencies, compared with those expected in the general population, are:

	Observed St -	Observed St +	Estimated Homozygotes	Estimated Heterozygotes
46 fathers ..	18	28	36	10
	Expected St -	Expected St +	Expected Homozygotes	Expected Heterozygotes
46 random Rh+ men	10-11	35-36	20	26

and in that case the homozygous fathers would be $\frac{36}{10} \times \frac{26}{10}$ —i.e., 4.68—times more dangerous than the heterozygous. The difference in distribution among the fathers and the normal population is highly significant statistically. Again, in a normal population of 46 Rh-positive persons 10 or 11 are expected to be St-negative and about 35 St-positive: that 18 fathers were St-negative and 28 St-positive is statistically significant.

Further evidence of the preponderance of homozygous fathers in affected families is given by the results of more recently discovered tests which determine certain Rh genotypes. The inheritance of the Rh groups is determined by a series of multiple allelomorphs, and by the use of different sera from the mothers of erythroblastotic babies the genotypes of about 80% of persons can be recognized. (See Race and Taylor, 1943; Race, Taylor, Boorman, and Dodd, 1943; Race, Taylor, Cappell, and McFarlane, 1944.)

Of the 46 fathers 38 were examined by tests which recognize the Rh₁rh and Rh₁Rh₂ genotypes. In the general population the frequency of Rh₁rh is about 33%—that is, about 40% of Rh-positives. Of 38 Rh-positive fathers, therefore, 15 would be expected to be Rh₁rh and 23 not Rh₁rh. But only 5 fathers were Rh₁rh—a highly significant departure from expectation, which shows a marked shortage of this commonest type of heterozygote. Thus:

	Rh ₁ rh	Not Rh ₁ rh
38 fathers: observed ..	5	33
38 random Rh+ men: expected ..	15	23

In 435 unselected donors the ratio of the genotype Rh₁Rh₂ to Rh₁rh was almost exactly 1 to 2; but of these 38 fathers 14 were Rh₁Rh₂ and 5 Rh₁rh—again a highly significant shortage of Rh₁rh.

The tests on the last 18 of the 46 fathers made it possible to recognize the following genotypes:

	Rh ₁ Rh ₁	Rh ₁ Rh ₂	(Homozygotes)	Rh ₁ rh	Rh ₂ rh or Rh ₂ Rh ₂	(Heterozygotes)
Observed	7	6	(13)	3	2	(5)
Expected	4	3	(7)	8	3	(11)

The serological tests do not yet differentiate between the genotypes Rh₁rh and Rh₁Rh₂, but, assuming the two fathers in this group are heterozygotes, then there are 13 homozygotes and 5 heterozygotes, whereas 7 and 11 would be expected in the general population: the discrepancy is on the verge of statistical significance. The 18 fathers have 23 Rh₁ genes to 8 Rh₂ genes—practically the same ratio, 41 to 15, found in the general population. This suggests that both genes are equally effective in producing the disease.

It may be thought that the manner of ascertainment has been responsible for the high proportion of homozygous fathers found in our sample, and that the diagnostic support given by a history of more than one jaundiced baby may make a doctor the more likely to send us blood samples and thus

prejudice our series in favour of homozygous fathers. This difficulty can be overcome if we consider fathers of families in which only one child is erythroblastotic. There are 26 such; 9 of them are St-negative—a proportion not very different from that found in the remaining families with 9 St-negative fathers out of 20. Twenty of the fathers of families with a single affected child were examined by the tests which recognize Rh₁rh and Rh₁Rh₂, and they show a significant shortage of Rh₁rh, there being only 2 instead of the expected 8, while the ratio of Rh₁rh to Rh₁Rh₂ is 2 to 7 instead of the expected 6 to 3.

Conclusions and Summary

The findings reported prove that there is a marked preponderance of homozygous fathers in families affected by haemolytic disease of the newborn; the homozygote appears to be about four or five times more dangerous than the heterozygote. This predominance of homozygotes affects enormously the chances of Rh-negative, and therefore unaffected, children being born. The genotype of about three-quarters of Rh-positive people can be determined serologically, and unless it can be shown that the father is heterozygous in this way, or by his having an Rh-negative child or an Rh-negative parent, the prognosis is entirely unfavourable.

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Medical Memoranda

Latent Malaria presenting as Anaemia

Anaemia is a well-known feature of malaria, both during the acute phase of the disease and in convalescence. Treatment by iron is not by any means always necessary, but in most cases is quickly curative. An anaemia, nevertheless, may occur which is both iron-resistant and susceptible to antimalarial therapy, at a time when the parasite would not normally have been suspected as the causative factor. Two such cases of anaemia are here reported. Response to antimalarial treatment was immediate and satisfactory in both cases.

CASE I

During Oct., 1942, this man had a first attack of clinical malaria which was apparently successfully cured by the usual course of treatment (quinine-mepacrine-pamaquin), but ever since then he had complained of general weakness, occasional cough, pains in the joints, and loss of weight. There were no rigors or sweats, and he was apyrexial. He was seen as an out-patient on Dec. 30—two months after his initial illness—when his condition suggested a blood count. This showed: R.B.C., 3,170,000; Hb, 70% (Sahli); C.I., 1.1; W.B.C., 5,100—polymorphs 38%, lymphocytes 56%, monocytes 6%.

He was admitted to hospital five days later. Detailed physical examination revealed a young man in poor condition and with marked pallor. Temperature 99°; pulse 80. Tongue furred; throat clear. Heart normal in size and position; rhythm regular. On auscultation there was a widespread systolic murmur, best heard along the left border of the sternum. B.P. 120/60. The lungs showed no abnormality. The liver was palpable and tender. The spleen was not palpable. Blood films for malaria parasites were persistently negative.

X-ray films of the chest showed no abnormality. On Jan. 1, 1943, a blood count gave: R.B.C., 3,640,000; Hb, 90% (Sahli); C.I., 1.2; W.B.C., 6,000 (polymorphs 53%, lymphocytes 42%, monocytes 3%, eosinophils 2%). Intensive iron therapy was instituted (ferri et ammon. cit. gr. 120 per diem). After one week the red cells had diminished by 20,000 and the Hb by 10%. Symptoms were not diminished, and his condition was unchanged. Some days later he suddenly developed an acute pyrexial illness, during which M.T. parasites were found in the blood film. Iron was discontinued and antimalarial treatment given. At the end of the treatment the red cell count had risen to 4,390,000, and when the patient was discharged fit and symptom-free a few days later this number had reached 5,500,000, with 96% Hb and 12,200 white cells, although anti-anemic treatment by iron had not been reinstituted.

CASE II

A prisoner of war, 42 years old, admitted to hospital on May 11, 1943, complained of weakness, headache, and slight diarrhoea. There was a history of ten attacks of malaria in the previous five years.

On examination the patient was found to be pale but not icteric. Temperature normal; tongue coated. Some petechial spots were