

THE USE OF SULFAGUANIDINE IN ENTERIC INFECTIONS

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IN THE summer of 1940 Marshall and his associates¹ published an experimental study on sulfaguanidine. This drug has the unusual property of being fairly soluble in water but poorly absorbed from the intestinal tract. Due to this it is possible to produce a high concentration (200 mg. per cent) in the intestinal tract but a relatively low concentration (1 to 4 mg. per cent) in the blood. This drug should therefore, theoretically, be useful in combating enteric infections. Later, Marshall and his co-workers² reported the use of this compound in the treatment of acute bacillary dysentery. In their series there were seventeen patients with no controls.

Following this, Lyon³ reported the use of this drug in the treatment of twenty-three patients with acute bacillary dysentery with an equal number of controls. Alternate patients were treated. Not all the patients were hospitalized, and stool cultures were done on approximately one-half of the patients.

FOREWORD

Bacillary dysentery is endemic in the eastern part of Kentucky. The number of cases varies widely from year to year but had shown a slight decline until the spring and summer of 1941, when the disease assumed epidemic proportions. This in part was due, no doubt, to a very dry season with a very occasional hard rain. Most of the patients came from the rural sections and mining camps where sanitation is not well advanced. According to the records of the Johnson County Board of Health, 50 per cent of the water supply of the rural areas shows pollution.

Acute gastroenteritis and bacillary dysentery still continue to lead all other diseases as a cause of mortality⁴ in preschool children in Kentucky.

There has been a marked decline in the incidence of typhoid fever in eastern Kentucky due to the efficient work of the county health departments. Of the five patients with typhoid in this study, all came from the same locality and four from the same family. All had refused immunization and all had used the same water supply which was later proved to be polluted. The diagnosis was usually confirmed by stool culture and the Widal reaction. None of the patients had had any previous immunization.

PROCEDURE

In the spring of 1941, through the cooperation of Dr. E. W. Kissel of the Johnson County Board of Health and Dr. F. W. Caudill of the

Division of Communicable Diseases of the Kentucky State Board of Health, sulfaguanidine* was used in the experimental treatment of the enteric infections.

During the spring and summer of 1941, thirty patients with acute bacillary dysentery were selected for treatment at the Paintsville Hospital. Only those patients were selected who were moderately to severely ill. The basis for this classification was the general appearance of the patient, the degree of temperature, and the character and frequency of the stools. Of these three, the degree of temperature is the least reliable as a guide. As pointed out by Lyon,⁵ dysentery is a disease with many vagaries. Often a child develops a temperature of 103 to 105° only to have the temperature return to an essentially normal level after two or three days although he may continue to have frequent stools containing blood and pus for one or two weeks.

Only those patients having diarrhea with a positive stool culture for the dysentery bacilli have been included in this series. The type of organism has, with one exception, been Hiss-Y dysentery. The Flexner organism, which has been encountered so frequently elsewhere,⁶ was not found in this series.

Of these 30 patients with dysentery, 15 have received sulfaguanidine and the other 15 were used as controls.

In addition to the above dysentery cases, 5 patients with typhoid fever and 1 with *Salmonella* gastroenteritis have received sulfaguanidine. This organism was identified as *Salmonella paratyphi B* var. *java* by Edwards⁷ of the National Salmonella Center of Lexington, Ky.

A detailed record has been kept on all patients. Of the 30 dysentery cases, all but 5 occurred in infancy and early childhood.

DOSAGE

The dosage followed has been that used by Lyon;³ namely, 0.1 Gm. per kilogram of body weight for the initial dose, followed by 0.05 Gm. per kilogram every four hours. When the stools became less than five in twenty-four hours, 0.05 Gm. per kilogram was given every eight hours for forty-eight to seventy-two hours. This dosage has been followed with few exceptions.

In the typhoid cases, an initial dose of 0.1 Gm. per kilogram was given, followed by 0.05 Gm. per kilogram every four hours for one week.

The drug was practically tasteless and not unpleasant to take. It was usually given in a suspension of water.

On this dosage schedule there was one relapse to which more reference will be made in the appendix of case reports (Case 8-A). In one instance the drug was discontinued after sixty hours (Case 1-A) without a relapse.

*The author wishes to express his appreciation to the Lederle Laboratories for supplying the sulfaguanidine used in this study.

Sulfaguanidine was usually started immediately in those cases in which there was blood and pus in the stools and in which the diagnosis was reasonably certain. However, in those cases in which there was no blood or pus and the diagnosis was not well established, a positive stool culture was required before starting the drug. This was necessary in only two instances.

BLOOD CONCENTRATION OF SULFAGUANIDINE

Every patient treated with sulfaguanidine had at least one determination of the blood concentration. The method used was that originally recommended by Bratton and Marshall,⁸ using 2 c.c. of blood. The concentration ranged from 1 mg. per cent to 3.6 mg. per cent. The average was 2.3 mg. per cent of the free drug. This was on a dosage schedule of 0.05 Gm. every four hours.

THE STOOLS

In order to get a composite picture of the character of the stools, at least one specimen was examined daily, and more when possible. The stools were regarded as checked when they numbered four or less in twenty-four hours, were formed, and contained no gross blood or pus. In the patients treated with sulfaguanidine, it was usually fairly easy to decide when the stools were checked, but in the control group the dividing line was never clear-cut and it was not always easy to decide. In several of the patients stool cultures were still positive after sulfaguanidine was discontinued.

As soon as possible after admission a stool specimen was sent to the laboratory and it was plated immediately on desoxycholate citrate agar and desoxycholate agar. These media were used because it was felt that they were superior to other media for the isolation of the dysentery bacilli. Usually three cultures were taken before the stool was called negative. Identification of the particular organism was completed by their carbohydrate fermentation reactions and agglutination with specific sera.

GENERAL TREATMENT

Both groups have received identical treatment except that no sulfaguanidine, sulfathiazole, or other sulfonamide compound has been given in the control group. No laxatives have been permitted. Pain, restlessness, and tenesmus were controlled by phenobarbital and camphorated opium. No bismuth preparations were used because they would have obscured the character of the stools.

In addition to the usual supportive measures, special attention was given to maintaining a good fluid intake, correction of acidosis, and insistence on a high vitamin intake. Many of the oral fluids were given as 5 and 10 per cent dextrose in physiologic saline. Acidosis was corrected by the use of either sodium bicarbonate or sodium lactate.

The diet was essentially a high protein, low carbohydrate, as protein milk, skimmed boiled cow's milk, or lactic acid milk. Temperatures were taken rectally except in adults. The temperature was recorded as normal when it remained constantly below 100.4° rectally and 99.4° orally. The admission temperature was the highest temperature recorded in the twenty-four hours following admission.

A blood count and urinalysis have been done at frequent intervals, usually daily. It has not been possible to do follow-up studies to detect any toxic effects of the drug.

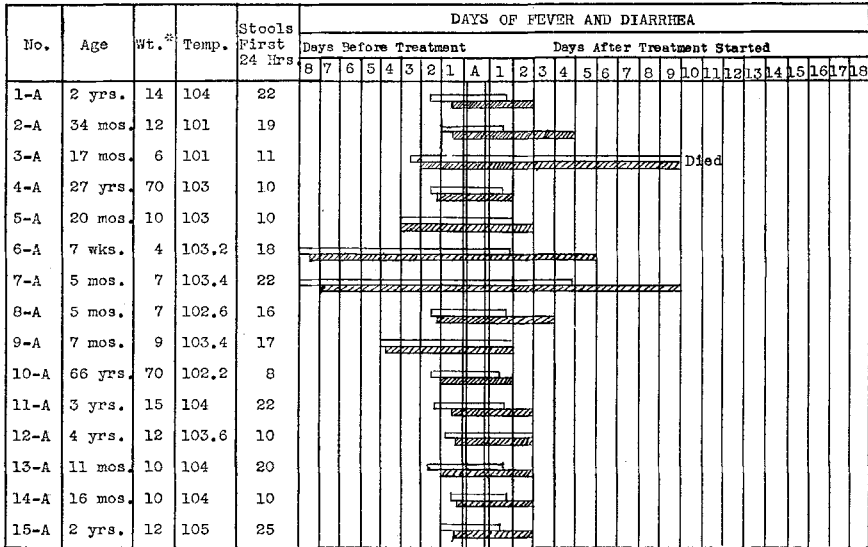
In the typhoid cases particular attention was given to maintaining a high caloric intake. Pain and restlessness have been controlled by the use of opiates. The *Salmonella* gastroenteritis was treated the same as the dysentery cases.

CLINICAL OBSERVATIONS

Of the fifteen patients with dysentery treated with sulfaguanidine the results in thirteen were excellent, only fair in one (Case 7-A), and a complete failure in another (Case 3-A). In most cases the response was just as dramatic and spectacular as that obtained by the use of sulfathiazole and sulfapyridine in pneumococcal pneumonia. The temperature usually dropped to normal in twenty-four hours, and the general appearance of the patient changed from that of an acutely ill child to one who could scarcely be called ill in a period of forty-eight hours. When treated early there was usually a definite decrease in the toxicity of the patient and a slowing down of the stools by as early as twelve hours, and practically always by twenty-four hours. The remarkable improvement in the general condition of the patient was the most dramatic thing observed in this study. Often a child who was acutely ill on admission would be sitting up in bed and playing in thirty-six hours. In all but three patients the temperature returned to normal in twenty-four hours.

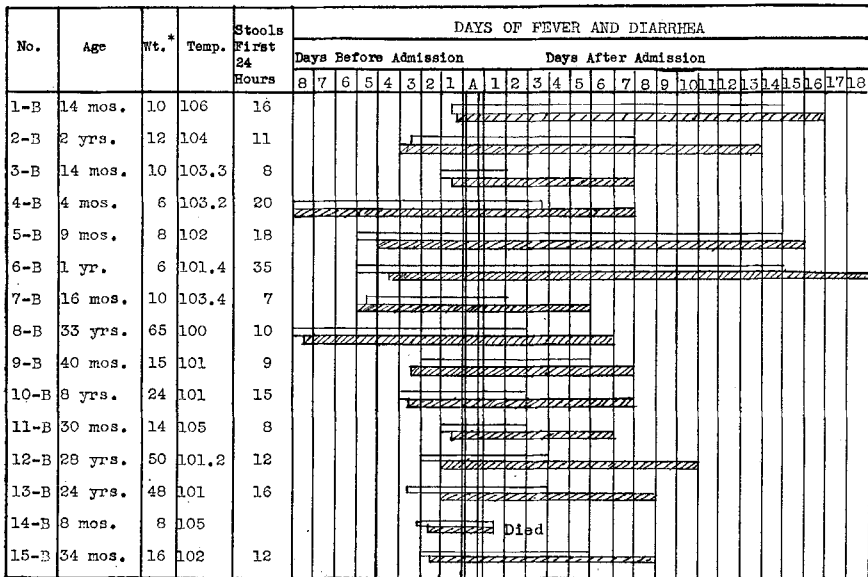
In one patient sulfaguanidine had no effect on the course of the disease and the child died on the ninth day (Case 3-A). He was a very poorly nourished male infant, 17 months old, weighing only 6 kilograms. The patient in Case 7-A was not admitted until the eighth day of the disease, and while he received some benefit from sulfaguanidine, improvement was slow.

A general idea of the differences between the two groups can be seen by comparing Charts 1 and 2. In general, the patients in the control group followed the course of the disease which has been observed in the past; however, there have been some rather wide variations. One patient died from an overwhelming toxemia only sixty hours after onset of illness (Case 14-B), while another patient made a very rapid recovery after an onset which would ordinarily indicate a virulent infection (Case 11-B).



Fever
 Diarrhea
 * - Weight in kilograms
A - Admission

Chart 1.—Dysentery patients given sulfaguanidine.



Fever
 Diarrhea
 * - Weight in kilograms
A - Admission

Chart 2.—Dysentery patients not given sulfaguanidine.

Of the five patients with typhoid treated with sulfaguanidine, all ran a course essentially unchanged by administration of the drug. In no instance was there any marked change in the temperature or improvement in the general condition of the patient. Two of these patients had a very stormy course. One patient who was pregnant aborted in the fourth week of the disease. This was followed by two postpartum hemorrhages which required two transfusions to correct; she was not discharged until the seventh week. The other patient had repeated small hemorrhages.

The patient with the *Salmonella gastroenteritis* ran a course which was unaltered by administration of sulfaguanidine.

While the number of typhoid cases is too small to draw any definite conclusions as to the effectiveness of the drug in these conditions, it would indicate that very little is to be expected from the use of sulfaguanidine in the typhoid-paratyphoid infections. Its final status in enteric infections can be determined only by clinical use and study.

TOXIC EFFECTS

Very few toxic effects have been observed in this series of twenty-one patients. In one patient (Case 1-A) a tide of sulfaguanidine crystals appeared in the urine after forty-eight hours of therapy. No hematuria was associated with the crystals. After sixty hours the drug was discontinued and fluids forced. No other untoward effects were observed in this case.

Nausea was observed in two instances. This cleared, however, as soon as the drug was discontinued. One other patient complained of a very severe headache which cleared as soon as the drug was discontinued. While sulfaguanidine was certainly not known to have been the cause, it was thought to have been. A unilateral conjunctivitis developed on the third day of therapy in one of the typhoid patients. None of the patients developed rashes or drug fever. The leucocyte count varied from 3,700 to 15,250. No tendency to leucopenia or agranulocytosis was noted.

No other toxic manifestations associated with the sulfonamide drugs, such as hematuria, hemolytic anemia, or anuria, were observed. However, it should be emphasized that sulfaguanidine was not given longer than twelve days in any case.

In general, toxic manifestations were encountered much less frequently than those observed in the use of sulfanilamide, sulfapyridine, and sulfathiazole.

CONCLUSIONS

Sulfaguanidine is an effective chemotherapeutic agent in the treatment of acute bacillary dysentery.

It is most effective when administered in the first few days of the disease.

While the number of typhoid patients treated has been too small to draw definite conclusions, indications are that very little is to be expected from the use of sulfaguanidine in typhoid fever.

In general, toxic manifestations were encountered much less frequently than those observed in the use of sulfanilamide, sulfapyridine, and sulfathiazole.

SUMMARY OF CASES TREATED WITH SULFAGUANIDINE

CASE 1-A.—P. B., a white female, aged 2 years, and weighing 14 kilograms, was admitted on the first day of illness. Chief complaints were high fever, a convulsion, and diarrhea. In the twelve hours before admission she had passed 12 stools, containing blood, pus, and mucus. She was acutely ill but not dehydrated. Temperature was 104° and white blood count, 9,350. A stool culture was taken and the patient was started on sulfaguanidine. Stool culture later revealed Hiss-Y type of dysentery. Her temperature dropped to normal in twelve hours and there was a marked improvement in the general condition in twenty-four hours. In forty-eight hours the child appeared practically well. The stools dropped from 20 in the first twenty-four hours to 1 in the next twenty-four hours. After receiving sulfaguanidine for forty-eight hours, a tide of sulfaguanidine crystals appeared in the urine. The drug was discontinued twelve hours later and fluids forced. No other toxic symptoms were noted, and the child was discharged on the seventh day.

CASE 2-A.—S. C., white female, aged 34 months, and weighing 12 kilograms, was admitted on the second day of illness. Chief complaints were fever and diarrhea. She was moderately ill and the history revealed that she had passed about 20 stools in the first twenty-four hours of illness, containing blood, pus, and mucus. Her temperature was 101° and white blood count was 15,050. Her stools contained more than the usual amount of blood, and the Hiss-Y type of organism was isolated from the stools. Sulfaguanidine was started immediately. Within eight hours her temperature was normal, and there was a very marked improvement in the general condition at the end of forty-eight hours. The improvement in the stools, however, did not parallel the improvement in her general condition, as they were not checked until the fifth hospital day. Sulfaguanidine was discontinued on the seventh day and the patient was allowed to go home on the same day.

CASE 3-A.—E. C., white, male, aged 16 months, weighed 6 kilograms at the time of his first admission. Chief complaints were fever and diarrhea. Five days before admission he had eaten some sandwich spread, containing pickles, olives, etc. Following this he began to have a diarrhea and fever. For the two days before admission he vomited everything taken by mouth and was reported to have had 30 loose, watery stools in the twenty-four hours before admission. At the time of admission he was very markedly dehydrated and critically ill. Carbon dioxide combining power was 28 vol. per cent. A continuous intravenous drip was started and sodium bicarbonate given to correct the acidosis. Within twenty-four hours he was much improved. Due to his very poor general condition, it was three weeks before he recovered. He was retained in the hospital two weeks longer to build up his general condition. Three stool cultures were negative and at no time during hospitalization was any gross blood or pus observed in the stools.

Second Admission.—He was readmitted eight days later with a history of a bloody diarrhea for two days. At this time he was acutely ill. Temperature was 101°. Sulfaguanidine was started immediately. The first stool culture was positive for

Hiss-Y dysentery. Despite sulfaguanidine, parenteral fluids, and repeated blood transfusions, his course was progressively downward and he expired on the ninth hospital day.

CASE 4-A.—V. C., white, female, aged 27 years, and weighing 70 kilograms, was admitted on the second day of illness. Chief complaints were fever and diarrhea. In the fifteen hours before admission she had passed 14 stools and the last few contained blood, pus, and mucus. Her temperature was 103° and she appeared acutely ill. The leucocytes numbered 8,200. She was started on sulfaguanidine immediately. Stool culture was positive for Hiss-Y dysentery. Her temperature returned to normal in eighteen hours and the stools dropped from 10 in the first twenty-four hours to none in the next twenty-four hours. There was marked improvement in her general condition in the first thirty-six hours. On the third and fourth hospital days she complained of a severe headache. This was thought to be due to sulfaguanidine. The drug was discontinued on the fifth day. No other toxic symptoms were noted. Patient was discharged on the sixth day.

CASE 5-A.—C. W., white, male, aged 20 months, and weighing 10 kilograms, was admitted on the fourth day of illness. Chief complaints were fever and diarrhea. In the twenty-four hours before admission he had passed 12 watery stools. No blood or pus was seen in stools. He was moderately ill. Temperature was 103°. White blood cell count was 9,100. Hiss-Y type of dysentery was isolated from the stools within forty-eight hours, and he was then started on sulfaguanidine. His temperature was normal in eighteen hours and he was practically well on the third day. The stools dropped from 15 on the first day that sulfaguanidine was started to 3 on the second day and never numbered over 4 thereafter. Sulfaguanidine was discontinued on the sixth day and he was allowed to go home on the eighth day.

CASE 6-A.—C. B., white, male, aged 7 weeks, and weighing 4 kilograms, was admitted on the eighth day of illness. Chief complaints were fever and diarrhea. He was reported to have had a watery diarrhea for eight days preceding admission. He was moderately ill. Temperature was 103.2°, and a leucocyte count was 10,700. Hiss-Y dysentery was isolated from the stools on the second day and he was then started on sulfaguanidine. His temperature returned to normal in twenty hours, but the diarrhea was not checked until the fifth hospital day. Sulfaguanidine was discontinued on the eighth day and he was sent home on the eighth day.

CASE 7-A.—L. P., white, male, aged 5 months, and weighing 7 kilograms, was admitted on the eighth day of illness. Chief complaints were fever and diarrhea. On admission he was very acutely ill and dehydration was marked. His temperature was 103.4°, and the white blood cell count was 10,650. He was reported to have passed 20 to 30 stools daily. There was a small amount of blood and pus present in stools. The first stool culture revealed the Hiss-Y type of dysentery. He was started on sulfaguanidine on the first day. His temperature did not return to normal until the fourth day, and there was only a very gradual slowing down of the stools, nine days being required before they had returned to normal. The improvement in his general condition, however, was slightly better than that observed on the stools and temperature. Sulfaguanidine was discontinued on the ninth day and he was allowed to go home on the tenth day. While the response to sulfaguanidine was certainly not as marked as in some other cases, it undoubtedly was beneficial.

CASE 8-A.—L. C., white, male, aged 5 months, and weighing 7 kilograms, was admitted on the second day of illness. Chief complaints were fever and diarrhea. He was admitted to the hospital moderately ill. Temperature was 102.6°, and a leuco-

cyte count was 10,000. In the twelve hours before admission he had passed 8 watery stools, containing blood, pus, and mucus, from which the Sonne type of dysentery was isolated. Sulfaguanidine was started immediately. Within a period of fourteen hours temperature returned to normal, and the general condition was much improved in twenty-four hours. Blood and pus did not disappear from the stools until the fourth day. The stools numbered 16 in the first twenty-four hours and never over 3 in any following twenty-four-hour period. He was practically well on the fourth day. Sulfaguanidine was discontinued on the seventh day, and he was allowed to go home.

Second Admission.—On the third day after going home his stools again became loose, and blood, pus, and mucus were present. He was readmitted two days later. At the time of second admission he did not appear very ill. Temperature was 99.8°, and leucocyte count was 8,100. Stool culture was again positive for Sonne dysentery. He was started on sulfaguanidine. The stools dropped from 7 in the first twenty-four hours to 2 in the next twenty-four hours and thereafter never numbered more than 1 daily. Blood was present until the sixth day. Sulfaguanidine was discontinued on the eighth day, and he was allowed to go home on the ninth day.

CASE 9-A.—S. S., white, male, aged 7 months, and weighing 9 kilograms, was admitted on the fourth day of illness. Chief complaints were high fever, and diarrhea. In the twenty-four hours before admission he had passed about 30 loose, watery stools, containing very little blood, pus, and mucus. He was acutely ill and slightly dehydrated. Temperature was 103.4°, and a leucocyte count numbered 7,850. Stool culture was positive for Hiss-Y type of dysentery. Sulfaguanidine was started immediately. Within a period of twelve hours he appeared brighter, and the stools were beginning to slow down. His temperature dropped to normal in twenty hours and he was practically well on the second day. The stools numbered 17 on the first day and dropped to 2 on the second day. He was taken home on the third day against advice; however, there was no relapse.

CASE 10-A.—S. J., male, aged 66 years, and weighing 70 kilograms, was admitted on the second day of illness. Chief complaints were fever and diarrhea. In the twelve hours before admission he had passed 8 stools, containing blood, pus, and mucus. He appeared moderately ill. Temperature was 102°, and a white blood count was 9,700. Stool culture was positive for Hiss-Y type of dysentery. Sulfaguanidine was started immediately. Within eight hours his temperature was normal. His stools numbered 8 on the first day and never over 2 on any following day. Sulfaguanidine was discontinued on the fourth day and he was allowed to go home.

CASE 11-A.—J. L., white, male, aged 3 years, and weighing 15 kilograms, was admitted on the second day of illness. Chief complaints were high fever, convulsions, and diarrhea. In the twelve hours before admission he had had three convulsions and was admitted while having the fourth. His stools contained blood, pus, and mucus. Temperature was 104°. White blood cell count was 7,950. After a short period of sedation he was started on sulfaguanidine. Within a period of ten hours there was a definite decrease in the toxicity, and his temperature was normal in eighteen hours. Stool culture revealed the Hiss-Y type of dysentery. Within forty-eight hours he was practically well. The stools numbered 22 in the first twenty-four hours and 2 in the next twenty-four hours, and blood was absent forty-eight hours after sulfaguanidine was started. Sulfaguanidine was discontinued on the fourth day and he was allowed to go home on the same day.

CASE 12-A.—J. P., female, aged 4 years, and weighing 12 kilograms, was admitted on the first day of illness. Chief complaints were convulsions, fever, and diarrhea. She was admitted to the hospital while having a convulsion. She was

reported to have had three other convulsions in the twelve hours before admission. She was having frequent bloody stools from which Hiss-Y type of dysentery was isolated. Her temperature was 103.6° and a leucocyte count was 10,200. Sulfaguanidine was started. Within eight hours there was a marked drop in temperature (100.4°) which was followed by a slight secondary rise. After forty-four hours temperature returned to normal. Her stools numbered 10 the first day and none the second day. The improvement in her general condition was rapid and she was well by the third day. Sulfaguanidine was discontinued on the fifth day, and she was allowed to go home on the sixth day.

CASE 13-A.—F. P., white, male, aged 11 months, and weighing 10 kilograms, was admitted on third day of illness. Chief complaints were fever and diarrhea. He was reported to have had 20 stools, containing blood, pus, and mucus, in the twenty-four hours before admission. Temperature was 104° and white cell count was 7,150. Sulfaguanidine was started immediately. Stool culture revealed the Hiss-Y type of dysentery. Within twenty hours his temperature was normal and he appeared well on the third day. His stools numbered 20 on the first day and 3 on the second day. Sulfaguanidine was discontinued on the fifth day and he was allowed to go home.

CASE 14-A.—J. M., white, female, aged 16 months, and weighing 10 kilograms, was admitted on the first day of illness. Chief complaints were fever and bloody diarrhea. She was admitted to the hospital after an illness of only ten hours. At this time she was passing very loose stools with a moderate amount of blood, pus, and mucus. The first stool culture was positive for the Hiss-Y type of dysentery. At the time of admission she appeared acutely ill. Her temperature was 104° and white blood cell count was 10,450. Sulfaguanidine was started. Within twelve hours her temperature had returned to normal and she appeared much better. She was well by the third day. Her stools numbered 10 the first day and 1 the following day. Sulfaguanidine was stopped on the fourth day and she was sent home.

CASE 15-A.—F. A., white, male, aged 2 years, and weighing 12 kilograms, was admitted on the second day of illness. Chief complaints were fever, a convulsion, and diarrhea. He was admitted to the hospital while having a convulsion. He was reported to have had about 25 stools, containing blood, pus, and mucus, in the twenty-four hours before admission. Temperature was 105° and a leucocyte count was 7,700. Stool culture was positive for Hiss-Y type of dysentery. Sulfaguanidine was started after a short period of sedation. Within eight hours his temperature had returned to normal and he appeared well on the third day. He had 20 stools on the first day and they did not exceed 4 on any day thereafter. Sulfaguanidine was discontinued on the fourth day and he was allowed to go home on the fifth day.

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