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The Use of Sulfaguanidine in Non-Specific Ulcerative Colitis and Other Infections of the Bowel

By

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INTRODUCTION

RECENT studies by Marshall and his coworkers (1) have suggested that sulfaguanidine may be useful in the treatment of infections originating in or confined to the intestinal tract. This compound was found to be fairly soluble in water, poorly absorbed from the bowel, and to reduce the number of coliform bacteria in the feces of mice. Preliminary observations by Marshall et al (2) and by Lyon (3) indicate that sulfaguanidine is of definite value in the early stages of acute bacillary dysentery. Sulfaguanidine has also been used successfully in the prophylaxis of infection following resection of the large bowel (4.) Therapeutic failures have been noted in a few instances of non-specific ulcerative colitis (5), chronic bacillary dysentery (2), and typhoid fever (2.) Our experience with this drug in a series of 20 patients is herein reported to enable further evaluation of sulfaguanidine as a chemotherapeutic agent.

METHOD OF STUDY

The series is composed of twelve patients with non-specific ulcerative colitis, two with lymphogranuloma venereum of the rectum, and two with bacillary dysentery, all of whom were studied at the Albert Merritt Billings Hospital; four additional patients with miscellaneous infections of the bowel were observed at St. Luke's Hospital. The sulfaguanidine* was administered in conjunction with the usual therapy employed in each case. The quantity of the drug used and the duration of treatment varied as noted in the individual case reports. The smallest amount given was 37.5 gms. in 10 days to a 2 year old infant with ulcerative colitis. The largest quantity administered was 1,132 gms. in 56 days to a 21 year old male with ulcerative colitis. In the majority of cases, 10 to 15 gms. of the drug were given daily in divided doses for a period of two to four weeks.

The investigative procedures in each case included examination of the feces for parasites, anaerobic culture of the stools for Bacterium Necrophorum (6), routine agglutination tests, the Frei reaction, and proctoscopic examination of the rectum and sigmoid. In addition, the following data was obtained every three to four days prior to and during chemotherapy; red and white blood cell counts, hemoglobin, differential smears, examination of the urine, and the concentration of free and total sulfaguanidine in the blood. Chemical analyses of the crystals obtained from 24 hour collections of urine in several cases were carried out at the Lederle Laboratories through the courtesy of Dr. David A. Bryce.

In fourteen of the sixteen patients studied at Billings Hospital, bacterial counts of the feces were made frequently before and during the administration of sulfaguanidine; the control period varied from 2 to 32 days. The procedure employed was as follows:

One gram of freshly passed feces was suspended in 9 cc. of sterile distilled water and shaken well with glass beads. Appropriate serial dilutions to 1-1,000,000,000 were prepared from which pour plates were made using both veal infusion and eosin methylene-blue agar. The latter media was employed to enable a more rapid evaluation of the lactose-fermenting organisms present. The plates were incubated at 37.5 degrees C. and the number of colonies per plate were counted. The total count was always made from the veal infusion agar plates since this media permits the growth of the more fastidious organisms. Typical colonies were stained and examined. In some instances further identification by special tests was carried out.

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*The sulfaguanidine was supplied in generous quantities by Dr. David A. Bryce, of the Lederle Laboratories, Pearl River, N. Y.
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TABLE I

Concentration of free and total sulfaguanidine in the blood (17 patients)

Case	Amount of Sulfaguanidine	Maximum Level (mg. %) Free	Total
A. N.	37.5 gms. in 10 days	*	2.4
L. C.	60.0 gms. in 10 days	1.3	1.8
P. M.	108.0 gms. in 11 days	2.9	4.3
F. T.	112.0 gms. in 11 days	2.9	4.2
L. P.	118.0 gms. in 12 days	3.3	4.2
C. H. B.	122.0 gms. in 13 days	3.7	4.8
L. M.	152.0 gms. in 10 days	1.9	2.2
J. C.	155.0 gms. in 14 days	5.2	5.4
R. N.	220.0 gms. in 17 days	—	5.1
M. R.	230.0 gms. in 16 days	—	5.0
B. R.	256.0 gms. in 34 days	4.0	5.5
S. D.	280.0 gms. in 21 days	—	6.5
I. D.	292.0 gms. in 29 days	5.0	6.1
M. C.	410.0 gms. in 28 days	9.2	10.8
G. R.	844.0 gms. in 90 days	6.8	8.0
J. F.	980.0 gms. in 66 days	9.2	10.3
B. A.	1132.0 gms. in 56 days	7.1	8.4

The values are presented as so many colonies per gram of feces. The concentration of sulfaguanidine in the feces was determined in two patients using the method elaborated by Marshall et al (2.)

RESULTS

(A) Concentration of Sulfaguanidine in the Blood and Feces.

The maximum concentrations of free and total sulfaguanidine in the blood are recorded in Table I. It will be noted that the levels were comparatively low in 13 of the 17 cases for whom data are available. This finding is in agreement with previous observations. Marshall (2) obtained average values for free sulfaguanidine in the blood of only 1.9 to 3.3 mg. % and values for total blood sulfaguanidine of 2.5 to 4.5 mg. % in a series of children and adults given varying quantities of the drug. Firor and Jonas (4) reported blood levels between 2 and 4 mg. % while Corwin (9) found that the blood concentration in dogs receiving large quantities of sulfaguanidine rarely exceeded 4 mg. %. However, in three patients of the present series the free sulfaguanidine rose to levels of 7.1, 9.2 and 9.2 mg. % and the total sulfaguanidine increased to 8.4, 10.3 and 10.8 mg. % respectively indicating that considerable absorption of the drug can occur during its prolonged administration in large quantities. The concentration of sulfaguanidine in the feces in cases M. C. and B. A. measured 4200 and 2800 mg. % respectively. Similar concentrations have been reported by Marshall and his associates (2.)

(B) Bacterial Counts of the Feces.

These counts in the fourteen patients who were studied in detail are recorded in Table II. It will be noted that the control values varied in the same patient as well as from one case to another. Usually from 3 to 18 days of chemotherapy elapsed before any appreciable change in the counts was noted. In no instance was a sterilization of the bowel accomplished. A significant decrease in the total count with a corresponding change in the flora from gram-negative bacilli to mainly gram positive cocci occurred in six patients. The bacterial content of the feces decreased in three cases but the flora was unchanged. In general, the larger the daily intake of sulfaguanidine the more frequently was there a decrease in the bacterial counts. In four patients the bacterial flora was altered but the total count was unchanged. In the remaining patient (L. C.) no alteration occurred either in the predominant type of organism or in the bacterial

TABLE II

Bacterial counts of feces before and during use of sulfaguanidine (14 patients)

Case	Amount	Before: Million Colonies Per Gram	Before: Type	During: Million Colonies Per Gram	During: Type	Decrease in Count
A. N.	37.5 gms. in 10 days	6200-9800	Coliform	2900-5100	G—cocci	+
L. C.	60 gms. in 10 days	104- 208	Coliform	104- 185	Coliform	0
P. M.	108 gms. in 11 days	6- 40	Coliform	6- 131	G—cocci	0
F. T.	112 gms. in 11 days	1000-1700	Coliform	0.2- 0.7	Coliform	++++
L. P.	118 gms. in 12 days	2200-4040	Coliform	1420-1760	G—cocci	++
C. H. B.	122 gms. in 13 days	1000-1300	Coliform	219	G—cocci	+++
L. M.	152 gms. in 10 days	870-6000	Coliform	110- 600	Coliform	+++
J. C.	155 gms. in 14 days	390- 560	Coliform	90- 477	G—cocci	+
B. R.	256 gms. in 34 days	1020-1040	Coliform	5- 9	G—cocci	++++
I. D.	292 gms. in 29 days	460- 750	Coliform	4- 9	G—cocci	++++
M. C.	410 gms. in 28 days	500-1080	Coliform	13- 95	G—cocci	++++
G. R.	844 gms. in 90 days	20- 52	Coliform	0.2- 0.9	G—cocci	++++
J. F.	980 gms. in 66 days	800-13,500	Coliform	0.3- 80	G—cocci	++++
B. A.	1132 gms. in 56 days	325- 490	Coliform	102- 706	Coliform	+++

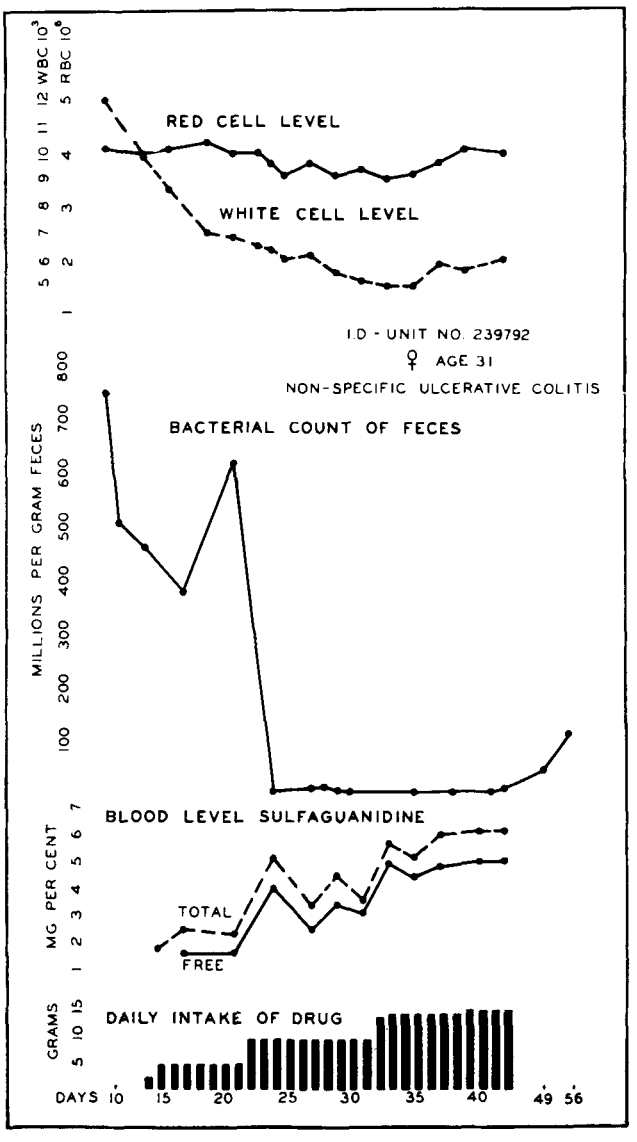

Fig. 1

count. The coliform bacteria in some instances were completely eliminated from the stools and did not appear even when plates were streaked directly from the fecal mass. In other instances, the coliform bacteria persisted in the highest concentrations but were not present in the highest dilutions. The predominant organism after the institution of chemotherapy usually was the green streptococcus, but staphylococci, gram-positive, spore-bearing bacilli, yeasts, and moulds also were present.

Bacterial counts made in several cases after the termination of treatment revealed a rapid increase of the coliform bacteria with a corresponding rise in the total count. Although too little of the drug was carried over in the dilutions employed to exert any possible bacteriostatic effect, it was considered of interest to ascertain whether para-amino-benzoic acid in vitro might counteract the effect of sulfaguanidine as it does with sulfanilamide. For this purpose, para-amino-benzoic acid was added to the various fecal dilutions in two instances; no alteration was produced thereby in the total count or in the relative proportion of the different bacterial types. Black et al (7) and MacKenzie et al (8) have reported, on the other hand, that para-amino-benzoic acid in vivo prevented the growth-inhibiting effect of sulfaguanidine in rats fed a purified ration.

The present findings are consistent with previously reported data. The most extreme change noted by Firor and Jonas was a decrease from 16,720,000 to 10,000 colonies after 14 days of chemotherapy. Corwin (9) found, on the other hand, that the administration of sulfaguanidine in dogs and monkeys did not produce a decrease in the total number of organisms in the feces; the gram positive bacteria, particularly the cocci, increased at the expense of the gram negative bacilli. This reversal of bacterial predominance occurred almost immediately and in some instances the gram negative bacilli apparently disappeared completely. Firor and Poth (10) observed a more frequent reduction in the number of coliform bacteria in the stool when the drug was given at frequent intervals throughout the day rather than in several large doses. Bornstein and Strauss (11) have shown that sulfaguanidine also is effective against S, cholera suis and to some extent against S. paratyphi A, but is ineffective against other organisms of the Salmonella group.

(C) Toxicity.

Few toxic reactions have been observed during sulfaguanidine therapy. A moderate decrease in the hemoglobin (not definitely attributable to the medication) was noted in three of 25 children given therapeutic doses of the drug (2); there was no hematuria, no effect apparent on the leukocyte count, no rashes, and no drug fever. In 25 adults receiving the drug for a variety of conditions, toxic reactions occurred or were suspected in three cases (2); (a) drug fever and unilateral conjunctivitis on the second day; (b)

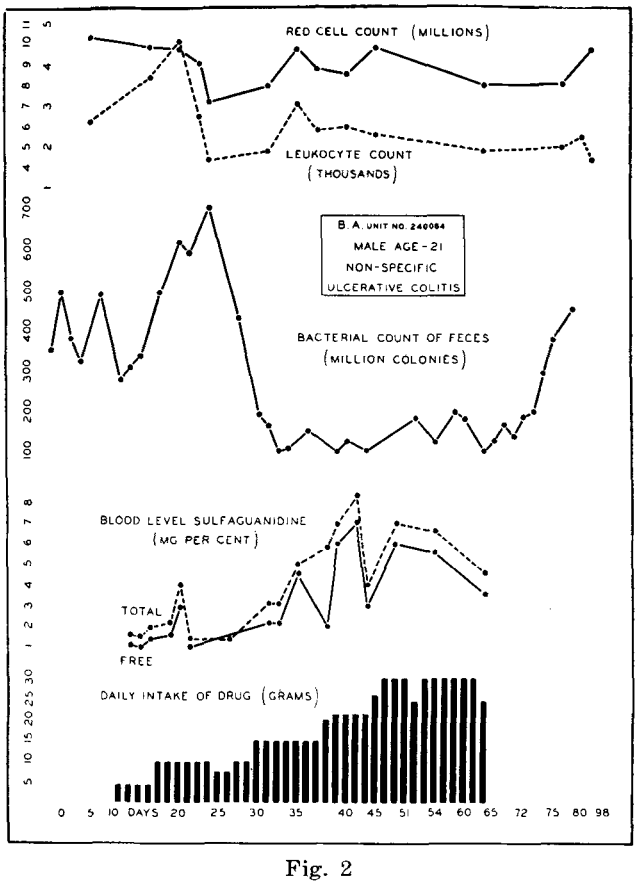

Fig. 2

possible mild leukocytic anemia on the third day, and (c) fever on the eighth day. No harmful effects have been reported by Lyon, and by Firor and Jonas. Firor and Poth (10) believe that while it is possible to reduce regularly the concentration of coliform organisms in the intestine, this cannot always be accomplished without the occurrence of high blood levels of the drug or the appearance of toxic symptoms. Mild toxic manifestations were noted by them in four of thirty-six patients receiving the drug. Corwin (9) found that "under ordinary conditions, any animal which absorbs sulfaguanidine poorly and does not acetylate it to excess, as the monkey, can ingest the drug over a relatively long period of time, at least four weeks, without ill effects."

Toxic reactions during the use of sulfaguanidine were observed in four patients of the present series. In case J. C. on the eleventh day of chemotherapy, after 131 gms. of the drug had been given, the blood smear contained a considerable number of toxic metamyelocytes such as are seen in agranulocytic reactions. During the next 48 hours these changes became more pronounced and all the cells of the polymorph series were toxic metamyelocytes. Coincident with this finding there appeared a partly scarlatiniform, partly morbilliform generalized skin eruption. The sulfaguanidine was discontinued and the dermatitis and toxic blood cells promptly disappeared.

In case G. R., after 106 gms. of the drug had been administered in 11 days, an erythematous, papular eruption appeared on the outer surfaces of both upper arms, associated with a generalized urticaria. The dermatitis subsided rapidly upon the discontinuation of the sulfaguanidine. This patient subsequently received more than 700 gms. of the drug without toxic manifestations.

In case F. T., a diffuse, erythematous, papular eruption appeared after 102 gms. of sulfaguanidine had been administered in 10 days. The dermatitis subsided rapidly after discontinuation of chemotherapy. Three days later when 2 gms. of the drug had been given, a similar rash quickly appeared, preventing the resumption of sulfaguanidine treatment.

In case L. M., after 92 gms. of the drug had been administered in 6 days, a symmetrical vesicular eruption, resembling erythema multiforme, appeared on the face. The dermatitis persisted for four additional days of continued chemotherapy but rapidly disappeared when the sulfaguanidine was discontinued.

In case A. N. there was one day of unexplained fever which subsided in 24 hours despite the continuation of therapy. In several cases there was an appreciable drop in the red blood cell counts. The leukocyte count frequently diminished to levels between 4000 and 5000 but, with the one exception noted previously, toxic granulopenia was not observed. The urine remained normal in every instance. Varying quantities of crystalline N_4-acetylsulfanilylguanidine were found in the urine in those cases in which it was sought for. There was no nausea or vomiting. Despite the reactions described above, sulfaguanidine appeared to be less toxic than other commonly used sulfonamides. The low toxicity of sulfaguanidine is well illustrated in patient B. A., who received 1,132 gms. of the drug without deleterious effects.

(D) Clinical Results.

1. *Non-Specific Ulcerative Colitis.*

Sulfaguanidine in varying dosage was administered to twelve patients with non-specific ulcerative colitis. The disease was arbitrarily classified as mild in one, moderately severe in five, and severe in six patients; one of this last group progressing to a fatal termination. In six patients clinical improvement had already taken place prior to chemotherapy and the drug was given primarily to study its effect upon the fecal flora. The clinical course in these six cases was unchanged in three and slightly improved in three. The following case report is a representative example of this group:

Case B. A. (Unit No. 240084) Fig. 2. A 21-year old male college student with a chronic nonspecific ulcerative colitis of 8 months' duration was admitted to the hospital acutely ill as a result of a severe exacerbation of symptoms. He was markedly dehydrated; there was tenderness and muscle rigidity over the lower abdomen. Examination of the stools for parasites, routine agglutination tests, and the Frei reaction were negative. Bacterium Necrophorum was isolated from anaerobic cultures of the stool. The rectal mucosa on proctoscopic examination was edematous, friable, and bled easily. The patient remained critically ill for several weeks; his temperature fluctuated between 99 and 104 degrees and the number of stools varied from 6 to 21 per day. Sulfanilamide in doses of 5.4 grams daily was given between the 14th and 20th hospital days without noticeable improvement. Treatment also included the use of sedatives, vitamins, and blood transfusions. The patient improved gradually during the next two months, although his temperature continued to be intermittently elevated. Sulfaguanidine therapy was started on the 60th hospital day and continued for 56 days; the daily dose was increased gradually from 4.8 to 9.6 grams, then to 15 grams, and finally to 30 grams daily; a total of 1,132.0 grams of sulfaguanidine was administered. There were no toxic symptoms or manifestations. The temperature returned to normal within 14 days. The number of stools decreased from 5 to 11 per day to 1 to 4 daily. The patient's body weight, which had decreased from 59.2 to 44.4 kg. during the acute phase of the illness, steadily increased to 56.2 kg. The rectal mucosa improved slightly; the edema and friability noted at the earlier examinations disappeared but the polypoid appearance and the bleeding persisted. There was no significant decrease in the red cell count directly attributable to the chemotherapy. The leukocyte count varied from 10,200 to 4,800. A few white cells were noted in the urine on several occasions but no other abnormal findings were observed except for the presence of crystalline N_4-acetylsulfanilylguanidine. Renal function, as determined by the urea clearance test, remained normal. The level of free sulfaguanidine in the blood increased from 1.0 to 7.1 mg: % and the total blood sulfaguanidine from 1.5 to 8.4 mg. %. There was a definite but possibly not significant decrease in the bacterial count of the feces. The control counts varied from 325 to 490 million colonies per gram while during sulfaguanidine therapy the values usually ranged from 108 to 201 million colonies per gram. The predominant organisms were gram negative bacilli of the colon group. The discontinuation of chemotherapy was followed by a steady increase in the bacterial content of the feces.

Comment: The clinical improvement noted in this patient occurred prior to the sulfaguanidine therapy.

No beneficial results were observed during sulfaguanidine therapy in five of the remaining six cases

with non-specific ulcerative colitis. Clinical improvement was noted, however, in one patient:

Case E. F. (Unit No. 217708.) A 32 year-old female textile chemist was admitted to the hospital with a history of intermittent diarrhea of two years' duration. The stools were watery and contained blood. Proctoscopic examination revealed a markedly granular mucosa which bled after cotton wiping. Routine agglutination tests, examination of the stools for parasites and the Frei test were negative. Bacterium necrophorum was isolated from anaerobic cultures of the feces. Roentgen studies revealed an advanced subacute stage of ulcerative colitis involving the entire colon and terminal ileum with multiple undermined ulcers in the ascending and transverse portions of the bowel. The patient remained in the hospital for five months and improved somewhat under a program of therapy comprising the use of a low residue, non-laxative diet, tincture of belladonna, and sedatives. The number of stools per day varied from 2 to 11 with an average of 6 movements; they were loose and contained varying amounts of blood. The patient subsequently was observed in the Out-Patient Clinic for two years. During this period there was no significant change in her condition. The number of stools per day ranged from 5 to 12; the rectal mucosa continued to appear granular although the contact bleeding had subsided. At this time, two years after her discharge from the hospital and four years after the onset of illness, the patient was given 10 grams of sulfaguanidine daily. After 14 days of chemotherapy, the patient stated that she felt better than at any time during her illness; the stools were still loose but their frequency had diminished to 1 to 2 daily. After 21 additional days of sulfaguanidine therapy the stools numbered only one daily; the granularity of the rectal mucosa had disappeared and the only evidence of previous inflammation was scarring of the mucosa.

It would appear from this study that sulfaguanidine is of no particular value in the management of non-specific ulcerative colitis. Since it is possible, however, that related "sulfa" compounds may prove beneficial in this disease, the continued trial of these drugs in the treatment of non-specific ulcerative colitis seems justified.

2. *Lymphogranuloma Venereum.*

Sulfaguanidine was ineffective in one patient with lymphogranuloma venereum complicated by pulmonary tuberculosis. It should be pointed out that the drug was not administered for a sufficiently long period of time to permit a conclusive appraisal of its efficacy. In the second case, chemotherapy was of definite, though not curative value, the clinical improvement being associated with a marked decrease in the bacterial count of the feces. This finding is in accord with the recent experimental observations of Rodaniche (12.) Sulfaguanidine, however, does not appear to have any advantage over other sulfonamides in the treatment of this condition.

3. *Miscellaneous Infections of the Gastro-Intestinal Tract.*

Chemotherapy was of slight, temporary value in one patient with a chronic Shigella Paradysenteria Flexner infection, and in a second individual with a fever possibly arising in a bowel infection. It was of no benefit in one patient with a Paratyphoid B infection and in another case with an infection of the biliary tract.

The present findings indicate that sulfaguanidine, when given in moderate amounts, is absorbed to a much less degree than are other sulfonamides. Considerable absorption of the drug does occur, however, after its prolonged use in large quantities. Sulfaguanidine exerts a variable effect on the aerobic bacterial flora of the intestine. In many instances, the number of coliform bacteria is markedly reduced resulting in a predominance of the gram positive cocci. In other cases, there is no appreciable change in the bacterial count or flora. The explanation for this variable effect is not apparent at present. Our observations, in agreement with previous studies, indicate that sulfaguanidine is less toxic than other commonly used sulfonamides. This property has been attributed by Richardson (13) to the poor absorption of the drug from the bowel and by Firor and Poth to its prompt elimination by the kidneys.

CONCLUSIONS

1. Sulfaguanidine, while not as readily absorbed from the intestine as other sulfonamides, is, nevertheless, absorbed to some extent. When doses of 10 to 15 grams are given daily, the blood levels may reach 10 mg. %.

2. Although reactions may occur during its administration, sulfaguanidine appears to be less toxic than other commonly used sulfonamides.

3. Sulfaguanidine, in doses of 10 to 15 grams daily, usually decreases the bacterial count of the feces markedly and transforms the flora from one predominantly coliform in type to one composed almost entirely of gram positive organisms.

4. Sulfaguanidine is of no value in the treatment of Paratyphoid B infection. It apparently has no advantage over other sulfonamides in the treatment of lymphogranuloma venereum. The long continued use of sulfaguanidine in chronic, non specific ulcerative colitis has not yielded any striking therapeutic results.

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