

PREVENTION OF RHEUMATIC FEVER BY TREATMENT OF PREVIOUS STREPTOCOCCIC INFECTIONS

EFFECT OF SULFADIAZINE

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For many years the sulfonamides were the only antibacterial drugs available for the therapy of acute streptococcal pharyngitis. Although such therapy was effective in reducing the duration of the illness and the incidence of the suppurative complications,¹ there is little information indicating whether or not it prevented the nonsuppurative complications, rheumatic fever and acute glomerulonephritis. In recent years, it has been demonstrated that the treatment of streptococcal infections with penicillin and other antibiotics will prevent the subsequent development of rheumatic fever.² Since many physicians continue to employ the sulfonamides in the treatment of streptococcal infections, it is important to establish whether such therapy will similarly prevent rheumatic fever. Therefore, in the present study, the treatment of acute streptococcal pharyngitis with sulfadiazine was evaluated with particular reference to the effect of such therapy on the attack rate of rheumatic fever.

METHODS

The clinical and laboratory methods employed have been described elsewhere.³ The present study was part of a larger investigation⁴ and included those airmen who were hospitalized with exudative pharyngitis or tonsillitis between April, 1953, and February, 1954. Excluded were all patients who gave a personal or family history of rheumatic fever, who had had a previous untoward reaction to penicillin or to sulfonamides, or who exhibited a suppurative complication at the time of the initial examination.

A total of 291 patients received 2 gm. of sulfadiazine initially, followed by 1 gm. every six hours for five days. Treatment was initiated on an average of 36 hours after the onset of symptoms, and for 92% of the patients therapy was started within 60 hours. A standard history and physical examination were recorded on admission and again 9, 13, 21, and 35 days after the onset of illness. Patients with manifestations suggestive of rheu-

• *Patients receiving sulfadiazine for acute streptococcal pharyngitis were compared with patients receiving other therapy for the same condition. The sulfadiazine reduced the incidence of complications during the acute phase. After the first week, however, the incidence of suppurative complications was about the same in both groups. The streptococci were not eradicated. The subsequent incidence of recurrent pharyngitis in the sulfadiazine group was three times that in the control group, and the sulfadiazine did not prevent rheumatic fever.*

matic fever were readmitted to the hospital for further observation. A culture specimen from the tonsils or oropharynx was obtained at the time of each examination.

The analysis was limited to 261 patients from whom group A streptococci were isolated at the time of admission to the hospital. Eighty-seven per cent of these patients harbored streptococci of types 3, 14, 19, or 30. Ninety-seven per cent of the patients were examined between 21 and 35 days after the onset of illness for evidence of rheumatic fever.

For purposes of comparison, a control group of 264 patients with exudative pharyngitis due to group A streptococci is included. These patients were selected and observed in the same manner as the patients treated with sulfadiazine, but they received only nonspecific therapy. Ninety-four per cent of the control patients were examined during convalescence. The two groups of patients appear to be comparable in that the historical and laboratory data obtained on admission were similar and the predominant serologic types of streptococci were the same. The control patients, however, were observed during the three-month period prior to the start of the present study.

RESULTS

In the dosages employed in this study, sulfadiazine did not eradicate the Streptococcus from the throat of patients with streptococcal exudative tonsillitis or pharyngitis (table 1). Nine days after the onset of symptoms, the infecting type of Streptococcus was isolated from more of the control patients than from those treated with sulfadiazine, which probably indicates continued suppression of the organism as a result of therapy. The carrier rates for the infecting type were equal in the two groups at 13, 21, and 35 days. Of those patients with bacteriological data available from all four examinations, the infecting type of Streptococcus was isolated at some time during the convalescent period from 88%

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of the group treated with sulfadiazine and from 93% of the control group. The acquisition rate for new types of streptococci was slightly less in the patients treated with sulfadiazine.

A recurrence of exudative pharyngitis or tonsillitis was observed in 21 of the treated patients (table 2). With one exception, the original infecting type of *Streptococcus* was again isolated at the time of recurrence of symptoms. The clinical relapse became manifest within one week after the completion of therapy in most instances. Therapy with one of the antibiotics was instituted in eight patients; four patients received no treatment during the relapse; and nine patients were given a second course of sulfadiazine. One of the latter patients subsequently developed rheumatic fever. In contrast, only seven patients in the control group developed a relapse, all of whom harbored the infecting type of *Streptococcus* at the time of the recurrence. One of these patients developed rheumatic fever following the second episode of exudative pharyngitis.

Suppurative complications, first recognized after at least 24 hours of therapy, were observed in 11 patients (4.2%) treated with sulfadiazine (table 2). In eight patients the complication developed after the comple-

of the drug in the elimination of the causative organism. As a general rule, with eradication of the organism the disease process will be terminated and complications will be prevented. Streptococcal infections differ from other infectious illnesses in that they are responsible for two nonsuppurative complications in which the infecting organism has not been directly related to the pathological lesions. These two diseases are rheumatic fever and acute glomerulonephritis. Recently, however, it has been shown that rheumatic fever develops after a streptococcal infection only if the organism persists in the oropharynx.⁴ Therefore, it would appear that the effect of therapy on the morbidity and complications of streptococcal infections can also be related to its effect on the infecting organism.

The results of this study would indicate that the administration of sulfonamides during the acute phase of streptococcal pharyngitis will reduce the incidence of suppurative complications. That such a reduction is related to the effect of the drug on the infecting organism is shown by the fact that the complications were prevented only during the period of therapy, when the growth of the *Streptococcus* was suppressed. Following the cessation of therapy and with the regrowth of the

TABLE 1.—Effect of Treatment on the Persistence of Group A *Streptococcus*

Type of <i>Streptococcus</i> Isolated at Convalescence as Compared with Admission Culture	Streptococcus Carriers, %							
	9 Days		13 Days		21 Days		35 Days	
	Sulfa-diazine	Control	Sulfa-diazine	Control	Sulfa-diazine	Control	Sulfa-diazine	Control
Same type.....	66	88	82	85	75	71	48	46
Different type.....	5	7	6	8	6	14	15	24
Group A <i>Streptococcus</i> not isolated.....	29	5	12	7	19	15	37	30

tion of therapy, whereas three patients manifested the complication between the third and fifth days of treatment. In the control group, 17 patients (6.5%) developed suppurative complications. During the first week of illness, 12 control patients and 4 treated patients developed suppurative complications, indicating that such sequelae were reduced by sulfadiazine during this period. After the first week the incidence of suppurative complications was essentially equal in the two groups.

A diagnosis of rheumatic fever was established in 14 of 261 patients who were treated with sulfadiazine, an attack rate of 5.4% (table 3). The interval from the onset of symptoms of pharyngitis to the onset of rheumatic fever was between 1 and 35 days in all instances, and the infecting type of *Streptococcus* was again isolated from all 14 patients after the onset of the rheumatic episode. In addition, there were six patients who developed manifestations that are frequently associated with rheumatic fever, but the symptoms were mild and subsided spontaneously. In the control group, 11 patients subsequently developed rheumatic fever, an attack rate of 4.2%. The interval to the onset of rheumatic fever was between 1 and 37 days, and the infecting type of *Streptococcus* was isolated from nine patients after the onset of rheumatic fever.

COMMENT

To evaluate an antibacterial agent in the treatment of an infectious disease, one criterion is the effectiveness

of the drug in the elimination of the causative organism. As a general rule, with eradication of the organism the disease process will be terminated and complications will be prevented. Streptococcal infections differ from other infectious illnesses in that they are responsible for two nonsuppurative complications in which the infecting organism has not been directly related to the pathological lesions. These two diseases are rheumatic fever and acute glomerulonephritis. Recently, however, it has been shown that rheumatic fever develops after a streptococcal infection only if the organism persists in the oropharynx.⁴ Therefore, it would appear that the effect of therapy on the morbidity and complications of streptococcal infections can also be related to its effect on the infecting organism.

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TABLE 2.—Recurrent Pharyngitis and Suppurative Complications Developing After at Least Twenty-Four Hours of Therapy

	Interval to Complication *				Total	
	2-7 Days	8-14 Days	15-21 Days	22-28 Days	No.	%
Sulfadiazine						
Recurrent pharyngitis.....	0	18	2	1	21	8.0
Suppurative complications						
Peritonsillar cellulitis.....	2	2	1	0	5	1.9
Otitis media.....	1	3	0	1	5	1.9
Sinusitis.....	1	0	0	0	1	0.4
Control						
Recurrent pharyngitis.....	2	4	1	0	7	2.7
Suppurative complications						
Peritonsillar cellulitis.....	9	3	0	0	12	4.6
Otitis media.....	2	1	0	0	3	1.1
Sinusitis.....	1	1	0	0	2	0.8

* Interval is from onset of acute illness to onset of complication.

nontreated patients. The relapse was apparently due to the original infecting type and in most instances required additional therapy. The most likely explanation is that sulfadiazine temporarily inhibited the growth of the *Streptococcus* and induced a remission in the manifesta-

tions of the disease. The reduction in the number of organisms presumably diminished the stimulation of antibody formation⁴ so that the patient did not develop immunity to the infecting Streptococcus. After therapy was completed, the organism again proliferated and a clinical relapse occurred.

Although acute pharyngitis or tonsillitis due to group A streptococci can be a prolonged and serious disease, particularly when suppurative complications supervene, the acute condition is seldom life-endangering or permanently disabling. For this reason, the primary concern in the treatment of such infections is the prevention of the nonsuppurative complications, rheumatic fever and acute glomerulonephritis. In the present study, the attack rate of rheumatic fever in the patients treated with sulfadiazine was slightly greater than in the control patients and was almost twice the usual incidence of 3%

apy should not be expected to affect the attack rate of rheumatic fever.

Rheumatic fever can be prevented by the use of antibacterial agents for prophylaxis against infection by group A streptococci or for therapy of the acute streptococcal illness.² The daily administration of sulfonamides or penicillin will prevent infection by group A streptococci,⁷ but the application of this prophylactic measure has been limited to special groups such as rheumatic subjects and military or institutional populations. Therefore, the only practical method available for the prevention of rheumatic fever in the general population is by therapy of the streptococcal infection itself. At the present time, it would appear that a single injection of benzathine penicillin G is the most effective means of preventing rheumatic fever in the patient with acute streptococcal pharyngitis.⁸ Other forms of penicillin,

TABLE 3.—Nonsuppurative Complications Occurring in 261 Patients with Streptococcal Pharyngitis Who Were Treated with Sulfadiazine

Cases	Interval to Rheumatic Fever, Days	Joint Manifestations*						Carditis †	Fever ‡	Elevation of ESR §	Abdominal Pain
		P	R	T	S	Mult.	Mig.				
Definite Rheumatic Fever											
1.....	1	+	0	+	0	+	0	+	+	+	0
2.....	7	+	0	+	0	+	+	+	+	+	0
3.....	10	+	0	+	0	+	+	+	0	0	+
4.....	11	+	0	+	0	+	+	+	+	+	0
5.....	13	+	0	+	0	+	0	0	+	0	+
6.....	14	+	0	0	0	+	0	+	+	+	0
7.....	17	+	0	+	0	0	0	+	+	+	0
8.....	19	+	0	0	0	+	0	+	0	+	0
9.....	19	+	0	+	0	+	+	0	+	0	+
10.....	24	0	0	0	0	0	0	+	+	+	0
11.....	25	+	0	+	0	+	+	+	+	+	0
12.....	32	+	+	+	+	+	+	0	+	+	0
13.....	35	+	0	+	+	+	+	0	+	+	0
14.....	35	+	0	+	0	+	+	0	+	+	0
Possible Rheumatic Fever											
15.....	1	+	0	+	0	+	+	0	0	+	0
16.....	6	+	0	+	0	+	+	0	0	0	0
17.....	10	+	0	+	0	+	+	0	0	+	0
18.....	16	+	0	0	0	+	+	0	0	+	0
19.....	16	+	0	+	0	0	0	0	+	+	0
20.....	19	+	0	0	0	0	0	+	+	0	0

* P, pain; R, redness; T, tenderness; S, swelling; Mult., multiple; Mig., migratory.

† P-R interval of 0.22 second or greater, partial or complete auriculoventricular block, significant change in heart murmur, or pericardial friction rub.

‡ Temperature of 100.2 F (37.9 C) or greater.

§ Erythrocyte sedimentation rate 15 mm. or more in an hour by the Wintrobe method.

seen in untreated patients.⁵ The obvious inability of such therapy to prevent rheumatic fever is apparently due to its ineffectiveness in the eradication of the Streptococcus. Recent investigations have indicated that persistence of the Streptococcus is essential for the development of rheumatic fever⁴ and that therapy which prevents rheumatic fever also results in the elimination of the organism.⁶ Since treatment with sulfadiazine does not significantly reduce the convalescent carrier rate, such ther-

chlortetracycline, tetracycline, erythromycin, or oxytetracycline, administered for at least 10 days, are also effective. Sulfonamides should not be employed in the treatment of streptococcal infections.

SUMMARY

Two hundred sixty-one patients with exudative pharyngitis due to group A streptococci were treated with sulfadiazine for five days. Sulfadiazine did not eradicate the Streptococcus from the respiratory tract and did not prevent rheumatic fever. Sulfonamides, therefore, should not be employed in the treatment of acute streptococcal pharyngitis. It should be emphasized that sulfonamides employed in prophylaxis against infection with group A streptococci have proved to be of great value in the prevention of such streptococcal infections and that the drug should continue to be utilized as a prophylactic measure.

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