# SULFANILAMIDE IN TREATMENT OF SORE THROAT DUE TO HEMOLYTIC STREPTOCOCCI

## WITH CONTROLS

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In a previous study [1] it was found that approximately one fourth of the illness among the nurses under our care was due to tonsillitis and pharyngitis. Two thirds of these cases were caused by hemolytic streptococci. While this incidence of sore throat may be slightly higher than that in a similar age group of the general population, it is probably lower than the incidence among children. Because of the great frequency of this condition it is likely that as much sulfanilamide is administered for sore throats proved or presumed to be due to hemolytic streptococci as for any of the great variety of infections for which it seems to be useful. The medical literature abounds with reports on the use of this drug for hemolytic streptococcus pharyngitis and tonsillitis. Many workers report almost uniformly favorable results.[2] Others, while impressed with results of the use of sulfanilamide in other streptococcic infections, have noted little favorable effect in ordinary hemolytic streptococcus tonsillitis and pharyngitis.[3] Coburn and Moore [4] found that sulfanilamide administered to rheumatic subjects after the onset of streptococcic throat infections did not prevent recrudescences. However, in a series of eighty rheumatic children who were given the drug prophylactically seventy-nine escaped hemolytic streptococcus infection and signs of activity of rheumatic infection. Schenck,[5] in a review of the use of the drug in otolaryngology, points out that most observers report favorable clinical responses to the drug but that the carrier state was usually not much affected. In our search of the literature we were unable to find a single study in which there were adequate controls.

Our own series is not large but may be of some value because the sulfanilamide treated patients were compared in as many respects as lent themselves to statistical analysis with a group being treated under identical conditions but without this drug.

The present study was begun two years ago. The subjects were all nurses of Cook County Hospital and Evanston Hospital who contracted hemolytic streptococcus pharyngitis or tonsillitis while on duty. There were occasional accompanying infections of the nasal passages and sinuses—five among the sulfanilamide treated group, six among the control group. Only patients with severely inflamed throats, proved to harbor beta hemolytic streptococci and with fever, were selected for the study; alternate patients were treated with the drug. Of the thirty-one sulfanilamide treated patients only three had a temperature below 100 F. and all but five had exudate on the mucous membranes of the pharynx or tonsils. In the control series of thirty-six cases five had a temperature below 100 F. and all but four had exudates. Many patients originally in the treated series were excluded from the study because treatment was begun after the fifth day of illness or because the drug had to be stopped because of reactions before a therapeutic effect could be expected. Aside from the use of sulfanilamide the patients of the two groups were treated in exactly the same way, i. e. with rest in bed until the temperature had been normal at least three days, hot alkaline gargles and either codeine or acetylsalicylic acid for aching in the body. The patients were not given sulfanilamide until their cultures had been reported positive for hemolytic streptococci, so that on the average treatment was begun 2.8 days after onset. The average duration of sulfanilamide treatment was 5.6 days. The dosage varied slightly according to the tolerance of the patients for the drug, but the average daily dose was 3.6 Gm. (54 grains). On the first day from 5 to 6 Gm. (75 to 90 grains) was given, divided usually into four doses. After that from 0.6 to 1.0 Gm. (10 to 15 grains) was given at four hour intervals through the day until the drug was discontinued. The average blood level attained was 6.38 mg. per hundred cubic centimeters. Apparently our method approximated that used by Long and Bliss in a series of forty-six cases.[6] In their series, on the average treatment was begun 2.3 days after onset and the average duration of treatment was five days. These workers state that "a blood concentration of 4 to 6 mg. per cent of sulfanilamide is generally all that is needed, and in many instances the infection may be controlled with lower levels of the drug." They consider the proper dose for adults to be 1 Gm. (15 grains) every four hours day and night at the start. After one day of normal temperature they cut this dose in half, then rapidly decrease as convalescence is established. Long states that none of his treated patients had complications.

TABLE 1.—*Comparison of the Clinical Course of the Sulfanilamide Treated Group with the Group Receiving No Sulfanilamide*

| | Sulfanilamide Treated Group (31 Cases) | Control Group (36 Cases) |
|---|---|---|
| Average days ill before hospitalization | 1.4 | 1.9 |
| Average days of hospitalization per case | 11.6 | 9.9 |
| Average days off duty per case | 18.8 | 17.5 |
| Average days carrying hemolytic streptococci per case | 19.0 | 19.1 |
| Average leukocyte count | 14,130 | 15,986 |
| Average duration of fever (days) | 6.84 | 4.1 |
| Average highest fever | 102.2 | 101.5 |
| Average duration of exudate on throat | 5.4 | 6.1 |
| Average duration of subjective complaint of sore throat | 9.1 | 8.0 |
| Average duration of cervical adenopathy | 11.0 | 9.6 |
| Percentage of complicated cases | 42% | 31% |

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1. Rhoads, P. S., and Afremow, M. L.: Clinical and Statistical Study of Sore Throat in Young Adults, Arch. Path. **26:** 403 (July) 1938.

2. Long P. H., and Bliss, Eleanor A.: Para-Aminobenzenesulfonamide and Its Derivatives: Clinical Observations on Their Use in Treatment of Infection Due to Beta Hemolytic Streptococci, Arch. Surg. **34:** 351 (Feb.) 1937. Smith, Alexander: Chemotherapy of Streptococcal Infections, Particularly Streptococcal Tonsillitis, Lancet **2:** 1064 (Nov. 6) 1937. Gallagher, J. R.: Observations on the Therapeutic Value of Sulfanilamide in Beta Hemolytic Streptococcus Pharyngitis, Am. J. M. Sc. **194:** 830 (Dec.) 1937. Hagemann, P. O., and Blake, F. G.: Clinical Experience with Sulfanilamide in Treatment of Beta Hemolytic Streptococcus Infections, ibid. **195:** 163 (Feb.) 1938. McLaurin, J. G.: Sulfanilamide in Otolaryngology, Ann. Otol., Rhin. & Laryng. **48:** 23 (March) 1939.

3. Schnitker, M. A.: Sulfanilamide: A Review, New England J. Med. **218:** 503 (March 24) 1938. Lockwood, J. S.; Coburn, A. F., and Stokinger, H. E.: Studies on the Mechanism of Action of Sulfanilamide, J. A. M. A. **111:** 2259 (Dec. 17) 1938. Keefer, C. S.: Streptococcal Disease, New England J. Med. **220:** 109 (Jan.) 1939.

4. Coburn, A. F., and Moore, L. V.: The Prophylactic Use of Sulfanilamide in Streptococcal Respiratory Infections, with Especial Reference to Rheumatic Fever, J. Clin. Investigation **18:** 147 (Jan.) 1939.

5. Schenck, H. P.: Use of Sulfanilamide in Otolaryngology, Arch. Otolaryng. **28:** 698 (Nov.) 1938.

6. Long, P. H., and Bliss, Eleanor A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, Macmillan Company, 1939, p. 160.

RESULTS

Table 1 shows that in our study the clinical course of the sulfanilamide treated series was practically identical with that of the untreated controls. The complications of the sore throats in the two groups were also almost the same. A striking feature of pharyngitis and tonsillitis due to hemolytic streptococci is the profound

TABLE 2.—*Comparison of Complications in the Sulfanilamide Treated Group and the Control Group*

| | Sulfanilamide Treated Group (31 Cases) | Control Group (36 Cases) |
|---|---|---|
| Total number of complicated cases (exclusive of toxic reactions to the drug) | 13 | 11 |
| Paranasal sinusitis | 5 | 6 |
| Chronic carriers (beyond 14 days) | 11 | 11 |
| Otitis media | 2 | 1 |
| Mastoiditis | 2 (nonsuppurative) | .. |
| Severe asthenia incapacitating the patients more than one week after fever had subsided | 6 | 1 |
| Acute peritonsillitis | 1 (no abscess) | 2 (abscess) |
| Late recurrence of fever | 2 | .. |
| Rheumatoid arthritis | 2 | .. |
| Persistent pharyngitis over a long period | .. | 2 |
| Erythema multiforme | .. | 1 |

asthenia which so often incapacitates the victims for many days after the fever, cervical adenitis and other objective signs of active disease have subsided. This complication was much more frequent in our sulfanilamide treated group, possibly as the result of treatment. Those patients found to have positive cultures for hemolytic streptococci two weeks or more after the initial infection are listed in the series as "carriers." It will be seen that sulfanilamide did not influence the carrier state, there being eleven carriers in each group.

Cervical adenopathy occurs to some degree in nearly every case of streptococcic pharyngitis and tonsillitis. It is not considered a complication by us unless the adenopathy is thought to prolong the disability an unusually long time or unless suppuration occurs. Hence cervical adenitis does not appear as a complication in the tabulation of either series.

TABLE 3.—*Toxic Reactions to Sulfanilamide in Thirty-One Cases*

| | |
|---|---|
| Nausea and vomiting | 8 |
| Dizziness and headache | 4 |
| Rash | 4 |
| Leukopenia | 3 |
| Severe asthenia (in absence of other complications) | 2 |
| Precordial pain and bradycardia | 1 |
| Febrile reaction | 1 |
| Tinnitus | 1 |
| Hallucinations | 1 |
| Severe mental depression | 1 |
| Total number exhibiting toxic signs (cyanosis not included) | 16 |

REACTIONS TO SULFANILAMIDE

Some degree of cyanosis was observed in practically every case in which full doses of sulfanilamide were administered and was not listed as a toxic reaction in the tabulations. Table 3 shows that sixteen of the thirty-one sulfanilamide treated patients had one or more of the usual reactions to this drug. Nausea and vomiting were the most frequent reactions; leukopenia, precordial pain and hallucinations were the most alarming. These reactions subsided after withdrawal of the drug. Several other cases are not included in this series because severe toxic manifestations led to discontinuance of the drug before an adequate amount could be given.

SUMMARY AND CONCLUSIONS

In our series of thirty-one sulfanilamide treated patients and thirty-six controls treated under similar conditions but without sulfanilamide, this drug was not found to reduce the severity of the symptoms, shorten the period of incapacity, reduce the incidence of complications or reduce the duration of the carrier state. Toxic manifestations of the drug other than the usual cyanosis occurred in one half of the cases in which sulfanilamide was administered. In a few instances these reactions were serious enough to cause genuine concern.

It is not wise to make sweeping generalizations on the basis of one series of controlled cases. Sulfanilamide is a drug of proved value in severe infections of deep structures due to the hemolytic streptococcus. However, in the average uncomplicated case of tonsillitis or pharyngitis due to hemolytic streptococci the advisability of its routine use is questionable. Certainly no physician should be censured for withholding the drug in these conditions unless complications such as severe cervical adenitis, paranasal sinusitis, otitis media, mastoiditis or meningitis supervene.

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# THE PRODUCTION OF SULFAPYRIDINE RENAL CALCULI IN MAN

## FOLLOWING ADMINISTRATION OF SULFAPYRIDINE

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The great interest in the therapeutic use of sulfapyridine has brought forward a multitude of reports showing its efficacy in acute infections. These articles have been closely followed by observations on the toxic manifestations of the drug; apart from gastrointestinal disturbances and a tendency for blood destruction, emphasis must be placed on the effect on the kidneys.

In view of the fact that most of the absorbed drug is excreted by the kidneys, either in the pure or in the conjugated form, it is conceivable that, if precipitating factors are introduced, serious traumatic or mechanical effects might be produced. That crystals of sulfapyridine are precipitated in the kidney tubules and pelves in certain species of mammals has been shown by many observers.

Antopol and Robinson [1] were the first investigators to report the appearance of uroliths in monkeys, rats and rabbits following the oral administration of large amounts of sulfapyridine. These investigators also described changes in the kidneys and ureters secondary to the deposition of sulfapyridine crystals and stones. In the milder cases they found a simple calculous ureteritis and pyelitis causing hematuria, but in the more severe cases marked pyelonephritis producing definite nitrogen retention in the blood. The sulfapyridine stones were discovered to be nonopaque to x-rays, and of particular significance was their observa-

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1. Antopol, William, and Robinson, H.: Urolithiasis and Renal Pathology After Oral Administration of 2(Sulfanilylamino) Pyridine (Sulfapyridine), Proc. Soc. Exper. Biol. & Med. **40**: 428 (March) 1939.