THE PREVENTION OF STREPTOCOCCAL UPPER RESPIRATORY INFECTIONS AND RHEUMATIC RECURRENCES IN RHEUMATIC CHILDREN BY THE PROPHYLACTIC USE OF SULFANILAMIDE[1]

By ANN G. KUTTNER and GERTRUDE REYERSBACH

(From Irvington House, Irvington-on-Hudson, N. Y.)

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In a previous paper (1), the effect of streptococcal upper respiratory infections on groups of rheumatic children under close observation in a sanatorium was reported. It was found that during a three-year period no rheumatic relapses were observed in children who escaped streptococcal upper respiratory infections. Since, however, the total number of rheumatic recurrences was small, it seemed possible that the relationship of the streptococcal pharyngitis to the reactivation of the rheumatic process might have been accidental. To rule out this possibility, it was essential to study the effect of preventing streptococcal upper respiratory infections in rheumatic subjects by some means which had no immediate influence on the rheumatic infection itself. For this purpose, sulfanilamide was chosen, as most observers agree that this drug not only fails to benefit patients with active rheumatic fever, but actually tends to increase the severity of the rheumatic symptoms (2 to 4).

On the other hand, the observations of Coburn and Moore and of Thomas and her coworkers indicated that prophylactic doses of sulfanilamide were effective in preventing streptococcal upper respiratory infections, and that rheumatic patients, so protected, escaped rheumatic relapses (5 to 9). These authors, however, did not have an opportunity of comparing the patients who were receiving sulfanilamide with a control group living under identical conditions, where exposure to Group A hemolytic streptococci could be determined. It seemed worthwhile, therefore, to study the value of sulfanilamide prophylaxis in an institution where the patients were under daily observation and careful bacteriological studies could be made.

The type of community, routine procedures, and bacteriological methods used were the same as those previously described (1).

PLAN OF STUDY

During two successive winters, 1940 to 1941 and 1941 to 1942, the 108 rheumatic children at Irvington House were divided into 2 groups, matched as closely as possible in regard to age, sex, number of previous rheumatic attacks, and cardiac findings. Beginning in October 1940 and continuing until the following June, half of the children were given small daily doses of sulfanilamide.[2] The other 54 children served as controls. During the second winter, 1941 to 1942, 54 children were given sulfanilamide and 50 served as controls. Only children who showed neither clinical nor laboratory signs of rheumatic activity received this drug.

During the winter of 1940 to 1941, 78 per cent of the 108 patients were cases of possible and potential heart disease and 22 per cent had definite cardiac lesions. During the second winter, 1941 to 1942, the percentage of children in the group with organic heart disease was increased to 49 per cent.

Dosage of sulfanilamide

During the winter of 1940 to 1941, an average blood level of sulfanilamide of 2 mgm. per cent was maintained. In most instances, children weighing 75 lbs. or less were given 1 gram daily in 3 divided doses, at 8 a.m., 2.30 p.m., and 8.30 p.m. Children weighing 75 lbs. or more received 1.3 to 2 grams daily.

During the winter of 1941 to 1942, the dosage was decreased slightly so as to maintain an average blood level of 1.5 mgm. per cent. Samples of bloods for routine determinations of sulfanilamide

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[2] Sulfanilamide (Prontylin) for this study was donated through the courtesy of the Winthrop Chemical Company.

levels were taken once every 3 weeks, before the 8 a.m. dose. In a small number of cases, the sulfanilamide content obtained before the morning dose was compared with that obtained before the 2.30 p.m. or 8.30 p.m. dose, and it was found that the blood level of sulfanilamide maintained throughout the course of the day was remarkably constant.

Streptococcal upper respiratory infections in the control group, 1940 to 1941

In October 1940, a routine culture of one of the children in the control group showed large numbers of Group A hemolytic streptococci Type 15. This child did not complain or present symptoms or show a rise in antistreptolysin 0 titer. This type of streptococcus had not been present previously in the community and the source of this microorganism was not determined.

Between the end of October 1940 and the end of January 1941, 30 cases of pharyngitis associated with this type of streptococcus developed among the 54 children in the control group. As in epidemics previously reported, the spread of this upper respiratory infection was slow: 3 cases developed in October, 8 in November, 12 in December, and 7 in January. Sixteen of these 30 cases were of moderate severity, with rectal temperatures of 101° F. or more. Eight had very mild symptoms. Six children did not have complaints or symptoms; and the diagnosis of pharyngitis was based solely on laboratory data (routine throat cultures positive for streptococcus Type 15 accompanied by a rise in white blood count or followed by a rise in antistreptolysin 0 titer).

Incidence of rheumatic recurrence in the control group, 1940 to 1941

Following a latent period, varying from 3 to 21 days, 14 of these 30 children developed definite rheumatic recurrences. Three of these 14 children had originally been in the group taking sulfanilamide but were unable to tolerate the drug. They contracted the Type 15 streptococcus infection 4 days, 5 weeks, and 2 months, respectively, following the withdrawal of sulfanilamide.

Of these 14 children with definite rheumatic relapses, 4 had organic heart disease prior to these attacks and 10 did not. The rheumatic manifestations in 11 of these 14 patients (10 cases of possible and potential heart disease and 1 case of organic heart disease) were of short duration. Three children whose rheumatic symptoms persisted for several months had definite cardiac lesions.

Eight of the 14 rheumatic relapses followed pharyngitis of moderate severity. Four occurred in children who had mild upper respiratory symptoms, and 2 developed in patients in whom the diagnosis of the preceding pharyngitis was based only on laboratory data.

Four additional children of the 30 who had the Type 15 upper respiratory infection developed, following a latent period, distinct laboratory signs of rheumatic activity (leukocytosis and increased erythrocyte sedimentation rates which persisted for 1 month or more), but had no definite clinical symptoms, or changes in their X-ray or electrocardiographic findings, and therefore were classified as having questionable rheumatic recurrences. One of these children had received sulfanilamide originally but could not tolerate the drug; his routine throat culture revealed hemolytic streptococci 2 weeks after the withdrawal of sulfanilamide. He had no complaints or symptoms but his antistreptolysin 0 titer rose, and his erythrocyte sedimentation rate remained elevated for 6 weeks.

Streptococcal carriers in the control group, 1940 to 1941

Two children in the control group became carriers of streptococcus Type 15 without developing symptoms of any kind. The leukocyte count, erythrocyte sedimentation rate, and antistreptolysin 0 titer in these patients showed no changes.

Streptococcal upper respiratory infections in the sulfanilamide group, 1940 to 1941

Only one child in this group contracted pharyngitis due to streptococcus Type 15. She complained of sore throat and had a temperature ranging from 101.2 to 100° F. for 2 days; and her leukocyte count was elevated. The same dose of sulfanilamide was continued and she recovered promptly. Her erythrocyte sedimentation rate remained normal and no rheumatic sequelae developed. The sulfanilamide blood level was 2 mgm. per cent at the time of her infection.

Streptococcal carriers in the sulfanilamide group, 1940 to 1941

Ten children, who received the drug in whom an average blood level of 2 mgm. per cent was maintained, became carriers of Type 15 without showing either clinical or laboratory evidence of infection. It is of interest that none of these children developed pharyngitis when sulfanilamide was discontinued on June 1, 1941, although 6 of them were still carrying streptococcus Type 15 at that time.

TABLE I

The seasonal distribution of streptococcus Type 15 upper respiratory infections and incidence of rheumatic recurrences, 1940 to 1941

Seasonal stribution	Control group (54 children)			Sulfanilamide group (54 children)		
	Pharyngitis	Definite rheumatic recurrences	Questionable rheumatic recurrences	Pharyngitis	Definite rheumatic recurrences	Questionable rheumatic recurrences
October	3	0	0			
November	8	3	0			
December	12	5	4	1	0	0
January	7	6	0			
February	0	0	0			
Total	30	14	4	1	0	0

Results, 1940 to 1941

The contrast as shown in Table I between the incidence of streptococcal pharyngitis among the children in the control group and those receiving sulfanilamide was striking, 30 to 1. Not a single child who received the drug developed rheumatic manifestations, whereas 14 of the 30, or nearly half, in the control group, who had streptococcus Type 15 upper respiratory infections, showed definite rheumatic relapses, and 4 additional children had laboratory evidence suggesting a reactivation of the rheumatic process.

Streptococcal upper respiratory infections, 1941 to 1942

On October 21, 1941, a boy (H. B.) was admitted with mild upper respiratory symptoms. His admission throat culture was positive for Group A hemolytic streptococci of undetermined type.

Beginning October 26th and continuing until the middle of January 1942, 17 children in the control group of 50 developed pharyngitis due to a streptococcus which appeared identical with the strain isolated from H. B. Rabbits were immunized with this microorganism, designated as B35, isolated from one of these patients; and with their sera used in slide agglutination (Griffith) and anti M precipitin tests (Lancefield), the strains isolated from the 17 cases of pharyngitis, as well as the one obtained from H. B. on admission, were shown to represent a single serological type, designated as streptococcus B35 in the remainder of this paper.[8]

The spread of streptococcus B35 was more rapid than that observed in previous outbreaks of streptococcal pharyngitis: 6 cases occurred in October and 9 in November, followed by 1 in December and 1 in January. Thirteen of these 17 cases were of moderate severity with rectal temperatures of 101° F. or more. In 2 patients, the symptoms were mild. Two children had neither complaints nor symptoms and the diagnosis of pharyngitis was based on laboratory findings.

Incidence of rheumatic recurrences in the control group, 1941 to 1942

Following a latent period varying from 10 to 18 days, 9 of these 18 children developed definite rheumatic recurrences and one a questionable rheumatic recurrence. Of these 10 children with rheumatic manifestations, 6 had organic heart disease previous to these attacks and 4 were cases of possible and potential heart disease. The rheumatic recurrences in 4 of these 10 children were severe (pericardial friction rub, subcutaneous nodules, persistent high fever). Of these 4, 3 had organic heart disease prior to these attacks and one did not.

Streptococcal carriers in the control group, 1941 to 1942

Two children in the control group became carriers of the epidemic inducing strain, B35, without developing symptoms of any kind.

[8] As will be reported by E. Krumwiede, in a paper now in press, this strain has been accepted as a new type and has been given the provisional type number 36.

Streptococcal upper respiratory infections in the sulfanilamide group, 1941 to 1942

Only one child in this group developed pharyngitis due to streptococcus B35. At the time of infection, the sulfanilamide level in the blood was only 0.95 mgm. per cent instead of the usual 1.5 mgm. per cent. Following a latent period, this patient developed mild rheumatic manifestations, namely, a prolongation of PR interval from 0.15 to 0.23 second, a drop in hemoglobin and red cells, and an elevated erythrocyte sedimentation rate. These symptoms lasted 10 days. There was no increase in the size of the heart nor any changes in the heart sounds.

Streptococcal carriers in the sulfanilamide group, 1941 to 1942

Four children who received this drug, and in whom the sulfanilamide content of the blood was maintained at an average level of 1.5 mgm. per cent, became carriers of streptococcus B35.

TABLE II

The seasonal distribution of streptococcus B35 upper respiratory infections and incidence of rheumatic recurrences, 1941 to 1942

Seasonal distribution	Control group (50 children)			Sulfanilamide group (54 children)		
	Pharyngitis	Definite rheumatic recurrences	Questionable rheumatic recurrences	Pharyngitis	Definite rheumatic recurrences	Questionable rheumatic recurrences
October	7	4	0	0	0	0
November	9	4	1	1	1	0
December	1	1	0	0	0	0
January	1	0	0	0	0	0
Total	18	9	1	1	1	0

Results, 1941 to 1942

As shown in Table II, the contrast between the incidence of streptococcal pharyngitis among the children in the control group and those receiving sulfanilamide was again clear cut, 18 to 1. The difference in the incidence of definite rheumatic recurrences in the two groups was 9 to 1.

Toxic reactions

During the first year, 1940 to 1941, 10 of the 54 children who were started on sulfanilamide developed toxic reactions of sufficient severity to necessitate stopping the drug, and other children were substituted for them.

During the second year, 1941 to 1942, the group receiving sulfanilamide consisted of 23 children who had taken the drug during the previous winter and 31 new patients. Among these 31 children, 5 were unable to tolerate the drug. Thus, of the total of 100 patients given prophylactic doses of sulfanilamide, toxic reactions developed in 15.

Similar toxic reactions were encountered during the two successive years: namely, fever, nausea and vomiting, skin manifestations, and leukopenia. The age, weight, dosage, and symptoms of the 15 children who developed toxic manifestations are summarized in Table III.

The most frequent toxic reaction was fever, in several instances accompanied by abdominal pain and vomiting. This reaction developed in 7 patients between the 5th and 13th day of medication after 10 to 26 grams of the drug had been given.

Five children developed skin manifestations. In 4 of them, this symptom appeared between the 11th and 15th days of medication when 11 to 14.5 grams of sulfanilamide had been taken. In 2 children, the rash was erythematous and the leukocyte count and temperature remained normal. In 2 others, the rash was urticarial and was accompanied by leukocytosis. One of these 2 children was afebrile. In the other, the urticaria was less extensive and the drug was not discontinued immediately; but 2 days later, this patient developed a temperature of 103° F. and the medication was stopped. In the 5th child, Number 9, Table III, the rash was also urticarial but did not develop until the 31st day of medication when a total of 70 grams had been taken. This patient had a temperature of 100° F. and a slightly elevated leukocyte count.

Leukopenia developed in 3 patients, after 3 to 4 weeks, when they had received 21 to 28 grams of sulfanilamide. The total number of white blood cells, as well as the percentage of polymorphonuclears, decreased gradually.

Results obtained by retesting patients who had developed toxic manifestations

In order to prove that the symptoms or blood changes observed were really due to sulfanilamide, the drug was restarted in 9 of these patients after intervals of 8 days to 18 months.

TABLE III

Toxic manifestations induced by sulfanilamide

Case number	Patient			Weight	Daily dose	Symptoms	Day of appearance	Further observations	Blood level
	Name	Sex	Age						
			years	*lbs.*	*grams*				*mgm. per cent*
1	S.S. 3593	M	12	77	2	Fever 102° F., WBC 10,400	5	After 8 days restarted. After 0.6 grams, fever 101° F. and vomiting.	
2	H.C. 3607	F	11	66	1	Erythema, WBC normal	11	18 months later tolerated a total of 26.7 grams given in 31 days.	1.1
3	F.S. 3529	F	8	51	1	Erythema, WBC normal	12	Patient discharged.	
4	G.R. 3463	F	11	70	1	Urticaria, WBC 20,000	15	After 18 months restarted. Urticarial rash after 8 grams had been given in 12 days, WBC 13,300.	1.05
5	R.A. 3581	F	15	104	2	Fever 100.4° F., WBC normal	13	After 12 days restarted on 1 gram daily. Rash after 7 days. WBC 11,000.	
6	P.P. 3558	F	8	55	1	Leukopenia, WBC 3,000, PMN 27 per cent	28	After 16 days restarted on same dose. Leukopenia after 23 days.	1.8
7	M.M. 3596	F	11	73	1	Leukopenia, WBC 2,700, PMN 24 per cent	22	After 6 weeks restarted on same dose. Leukopenia after 22 days.	1.4
8	D.B. 3584	M	11	89	2	Fever 101.2° F., WBC 10,300, abdominal pain	6	After 13 days restarted on 1 gram daily. Fever 101.4° F., vomiting after 16 days.	
9	J.C. 3606	F	14	110	2	Urticaria, WBC 10,500	35	Patient not retested.	
10	H.M. 3577	F	13	106	2	Fever 100.6° F., WBC 11,300	5	After 1 month restarted on same dose. Fever 105° F., WBC 12,200 on 2nd day.	2.8
11	S.C. 3669	M	13	105	1.3	Fever 102.4° F., WBC normal	9	6 months later tolerated a total of 26.7 grams given in 31 days.	1.
12	V.C. 3670	M	12	107	1.3	Fever 101.8° F., WBC normal	8	After 36 days started on sulfadiazine 1 gram daily, well tolerated.	2.6
13	S.T. 3676	M	14	111	1.3	Fever 101.2° F., abdominal pain, WBC normal	10	After 4 days started on sulfathiazole 1.3 grams daily. Fever and abdominal pain after 20 days. After 12 days started on sulfadiazine 1 gram daily. Fever and abdominal pain after 22 days.	1.25
14	A.S. 3718	F	8	54	1.	Leukopenia, WBC 2,800, PMN 33 per cent	21	After 55 days started on sulfadiazine 0.7 grams daily. Well tolerated.	1.9
15	F.A. 3722	F	13	89	1.3	Urticaria, WBC 11,900 Fever 103° F.	11 13	After 26 days started on sulfadiazine 0.7 grams daily. Well tolerated.	2.

Two patients, Numbers 1 and 10, Table III, who had developed fever, again showed febrile reactions of greater severity in a shorter period of time. A 3rd patient, Number 5, Table III, who developed fever the first time the drug was given, showed an urticarial rash without an elevation of temperature within a shorter period of time, although a smaller dose of sulfanilamide was used.

Another patient, Number 8, Table III, who had developed fever and abdominal pain, again showed similar symptoms when a smaller dose was given. This time, however, the child tolerated a somewhat larger total amount (16 grams instead of 12), and the toxic manifestations took 10 days longer to appear.

On the other hand, patient Number 11, who had shown a febrile reaction considered to be due to the drug, was given sulfanilamide again after an interval of 6 months. Restarted on 0.3 grams a day, the dose was then gradually increased to 1 gram a day. This time the patient received a total of 26.7 grams in 31 days without developing symptoms of any kind.

Two patients, Number 2 and Number 4, who had developed rashes considered to be due to sulfanilamide, were retested after an interval of 18 months. Both children were started on 0.3 grams a day and the dose was then gradually increased to 1 gram a day. This time patient Number 2 received a total of 26.7 grams in 31 days without developing toxic manifestations; but the other child, Number 4, again developed urticaria and leukocytosis after receiving a total of 8 grams in 12 days.

Another patient, not included in Table III, is also worth mentioning. A boy developed an extensive, itching, urticarial rash after receiving sulfanilamide for 2½ months. He had no fever and the leukocyte count was within normal limits. This patient had no history of asthma, hay fever, or food allergy. The drug was discontinued and the urticaria disappeared within 48 hours. After 2 weeks, this boy was restarted on 0.3 gram of sulfanilamide a day. The dose was increased gradually to 1.3 grams a day and then maintained for 4 months with no untoward effect.

Two patients, Numbers 6 and 7, Table III, who had developed leukopenia, again showed similar changes in the blood picture, with the same dosage, in approximately the same length of time.

Thus of 9 children retested, 7 again developed symptoms and 2 did not. It may be that the reactions originally observed in these 2 patients were not due to sulfanilamide. On the other hand, it also seems possible that the toxic manifestations were transient and did not recur when the drug was given more slowly.

Four of the 5 children who could not tolerate the drug during the winter of 1941 to 1942 were subsequently given sulfadiazine.[4] One boy developed symptoms identical with those caused by sulfanilamide, namely, fever and abdominal pain. The other 3 children tolerated sulfadiazine.

General condition of children receiving prophylactic doses of sulfanilamide

The children who did not develop toxic manifestations within 5 weeks tolerated the drug well. There were no subjective complaints. In most instances, the patients continued to gain weight at the same rate as before medication was started. The weight gain in children receiving sulfanilamide was comparable to that of children in the control group. Cyanosis was noticeable only in a few light-complexioned patients.

Administration of sulfanilamide for two successive winters

Twenty-three children who had received sulfanilamide during the winter of 1940 to 1941 remained in the institution. The drug was discontinued on June 1st, 1941 and restarted in October 1941 without inducing toxic manifestations.

Minor transitory toxic reactions

Leukocyte count and hemoglobin determinations were made once a week on every child receiving sulfanilamide. The total red cells were determined every 2 weeks, or oftener when indicated.[5]

It was found that the hemoglobin of most children receiving sulfanilamide tended to fall slightly and remained at a level somewhat lower than normal throughout the course of treatment. When the drug was discontinued, the hemoglobin rose to its previous level. In one instance, a boy of 12 years, weighing 79 lbs., with typical mitral stenosis, received 1 gram of sulfanilamide a day. His hemoglobin dropped from 14.5 to 10.5 grams per 100 cc. during the first week of medication. At the same time, his hematocrit reading fell from 42 to 32 per cent and his red blood count from 4,820,000 to 3,100,000 cells. He had no complaints, no jaundice, and normal urine findings. His blood sulfanilamide level was 1 mgm. per cent. Since he had no clinical symptoms and because a blood level of 1 mgm. per cent was considered insufficient to protect him from streptococcal pharyngitis, the dosage was increased to 1.3 grams a day. Within a week his hemoglobin, hematocrit reading, and red blood count began to rise. Thereafter, his hemoglobin ranged between 13 to 14 grams and his red blood count between 3,900,000 to 4,510,000 cells.

Minor fluctuations in the total leukocyte count and percentage of polymorphonuclears were also observed. In most instances, these changes were no greater than those encountered from time to time among children in the control group. An outbreak of upper respiratory infections of unknown etiology, accompanied by leukopenia, occurred in the institution during April and May 1942. With a few exceptions, sulfanilamide was not discontinued. The fall in leukocyte count in children receiving sulfanilamide and that in the control group were equally striking. However, the leukopenia tended to persist for a slightly longer period in patients receiving the drug.

[4] Sulfadiazine was donated through the courtesy of Lederle Laboratories, Inc.

[5] The expense of the technical assistance needed for the hematological studies was carried in part by a grant from The Borden Company.

DISCUSSION

The effect on the incidence of rheumatic relapses of preventing streptococcal upper respiratory infections by the prophylactic use of sulfanilamide is reported. Small daily doses of the drug were given to half of a group of rheumatic children under close observation in a sanatorium from October until June, during 2 successive winters. The contrast between the incidence of streptococcal upper respiratory infections and rheumatic relapses in the treated and untreated groups was clear-cut. Of the 108 children receiving sulfanilamide, only 2 children contracted streptococcal upper respiratory infections, and only one of these 2 patients showed signs of rheumatic activity. Among the 104 children who served as controls, 48 contracted streptococcal pharyngitis, and 23 of these, or 48 per cent, developed definite rheumatic relapses, and 5 additional children had laboratory evidence or mild symptoms suggesting rheumatic activity. In accord with our previous experience, no rheumatic relapses were observed in children who escaped streptococcal upper respiratory infections (1).

Evidence that rheumatic relapses usually follow in the wake of upper respiratory infections associated with Group A hemolytic streptococci had been accumulating for many years. The high incidence of rheumatic fever and rheumatic recurrences following outbreaks of tonsillitis in schools and training camps, as well as in convalescent homes for rheumatic children (10 to 14), suggested that streptococci might play a role in the etiology of this disease.

It is now well known that rheumatic relapses follow mild as well as severe cases of streptococcal pharyngitis. The symptoms of the upper respiratory infection may indeed be so slight as to be completely forgotten by ambulatory patients at the time that the rheumatic manifestations appear. Even in convalescent homes, cases of streptococcal pharyngitis may be overlooked unless careful bacteriological and serological studies are made. It is not surprising, therefore, that some observers have been inclined to doubt the importance of the relationship between streptococcal pharyngitis and rheumatic fever.

With the advent of sulfanilamide, a specific means of preventing streptococcal upper respiratory infections in rheumatic subjects became available. The studies of Coburn and Moore, and Thomas and her coworkers, indicated that the prevention of streptococcal pharyngitis also prevented rheumatic relapses. However, nearly all the patients included in the series of Thomas, *et al.*, were more than 14 years of age, when the incidence of rheumatic recurrences tends to decline spontaneously. In Coburn and Moore's studies, most of the children were ambulatory and the degree of exposure to Group A hemolytic streptococci could not be determined so accurately as among patients living in an institution. In our series, the incidence of streptococcal upper respiratory infections was high among the children in the control group, and nearly 50 per cent of those so infected developed rheumatic sequelae. Our results are in accord with those mentioned above and suggest that in closed communities where the spread of streptococci is difficult to control, prophylactic doses of sulfanilamide are effective in preventing both streptococcal pharyngitis and rheumatic relapses. Furthermore, these studies, aside from showing the prophylactic value of sulfanilamide, indicate that the relationship between streptococcal upper respiratory infections and the reactivation of the rheumatic process is specific, and therefore establish the importance of Group A hemolytic streptococci as a factor in the etiology of rheumatic fever.

Although the course of rheumatic fever in certain individuals is insidious, severe cardiac damage is usually the result of repeated rheumatic relapses (15). The chief aim therefore of the physician who has rheumatic patients under his care, should be the prevention of rheumatic recurrences. The effectiveness of prophylactic sulfanilamide in preventing rheumatic relapses has been established by our findings as well as those of others. In considering any prophylactic measure, however, the inherent danger must be carefully weighed.

The two most serious toxic reactions which have been reported during the course of sulfanilamide therapy are: acute hemolytic anemia and acute agranulocytosis. To date, hemolytic anemia has not been described in patients receiving prophylactic doses of sulfanilamide.

One instance of a fatal acute agranulocytosis, however, has been reported by Stowell and But-

ton (16). A boy of 12 years developed this complication after receiving 0.6 gram three times a day for 29 days. Acute agranulocytosis is rare in patients receiving sulfanilamide therapy. It occurs most commonly between the 17th and 25th day of treatment but may appear as early as the 14th and as late as the 70th day, and is independent of dosage (17, 18). Acute agranulocytosis develops suddenly and probably represents a peculiar idiosyncrasy to sulfanilamide. The possibility of this complication in patients receiving prophylactic sulfanilamide must always be borne in mind and constitutes the greatest hazard of this form of treatment.

The incidence of toxic reaction in our series (15 per cent) was higher than that reported by Coburn and Moore (6). No serious reactions were encountered. Even though smaller doses were used during the second winter than during the first, the incidence of toxic reaction was not reduced. It is our impression that in most instances the development of toxic reactions is due to an idiosyncrasy of the individual, rather than to the size of the dose. Twenty-three patients who received sulfanilamide during two successive winters showed no evidence of sensitization when the drug was restarted after a lapse of nearly 5 months.

In one instance, a blood level of 2 mgm. per cent was insufficient to prevent streptococcal pharyngitis. A similar failure was encountered in a patient with a blood level of 0.95 mgm. per cent. It seems possible that the child with the level of 2 mgm. per cent who contracted the streptococcal infection, was either very susceptible to the particular streptococcus or that the infecting dose was unusually large. In most instances, a blood level of 2 mgm. per cent seems to be adequate. On the other hand, we are of the opinion that a blood level of 1 mgm. per cent is probably too low to be effective.

The ultimate value of prophylactic sulfanilamide can be determined only by protecting rheumatic individuals from streptococcal upper respiratory infections for long periods of time. The prolonged administration of any drug as toxic as sulfanilamide may eventually prove harmful even in patients who apparently tolerate the drug. Furthermore, individuals who have been protected against infection with Group A hemolytic streptococci for many years may be extremely susceptible to these microorganisms when sulfanilamide is withdrawn.

On the other hand, the prognosis in patients with severe rheumatic heart disease is so poor as to justify taking risks. In our opinion, at the present stage of our knowledge, the effect of the prolonged administration of sulfanilamide should first be tried in this type of case.

To date, no reports have appeared on the prophylactic use of sulfadiazine in preventing streptococcal upper respiratory infections; and our own experience is too limited to warrant drawing conclusions. It seems likely that this drug will prove as effective as sulfanilamide.

Although it now seems established that Group A hemolytic streptococci play a part in precipitating rheumatic recurrences, the mode of action of these microorganisms in this disease remains obscure. It is possible that as our knowledge of the immunological response of individuals to streptococcal infections increases, new methods of combatting streptococci, based on biological reactions rather than on chemotherapy, will be devised.

CONCLUSIONS

1. Streptococcal upper respiratory infections and rheumatic relapses in rheumatic children were prevented by the prophylactic administration of sulfanilamide.

2. Toxic manifestations of sufficient severity to necessitate the withdrawal of the drug occurred in 15 per cent of the patients.

3. Children, who did not develop toxic reactions, tolerated the drug well.

4. The effectiveness of sulfanilamide in preventing rheumatic recurrences indicates that infection with Group A hemolytic streptococci is an important factor in the etiology of rheumatic fever.

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