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ATTACK RATES OF STREPTOCOCCAL PHARYNGITIS, RHEUMATIC FEVER AND GLOMERULONEPHRITIS IN THE GENERAL POPULATION*

I. A Controlled Pilot Study of Streptococcal Pharyngitis in One Village

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SINCE the attack rate of rheumatic fever and of acute hemorrhagic glomerulonephritis after untreated infection due to Group A streptococci has been estimated at between 1.5 and 5 per cent¹⁻⁵ penicillin treatment has been widely recommended for the control of these late nonsuppurative sequelae. The attack rate of glomerulonephritis is even higher when related to Type 12 infections.⁶

The attack rate of both diseases has been determined primarily from epidemic studies conducted in more or less closed communities living under epidemiologic conditions not prevalent in the general population.

Several recent reports⁷⁻¹⁴ have suggested that rheumatic fever and glomerulonephritis occur less frequently after endemic streptococcal pharyngitis. In most of these studies, however, penicillin treatment was instituted for all the cases of streptococcal illness observed, and most studies were performed in groups of children of school age,^{7,11-13} in orphanages,⁹ in family studies^{8,10} and in the civilian practice of pediatricians.^{8,14} In other studies the diagnosis of streptococcal pharyngitis was not bacteriologically confirmed,¹⁵ and in most no data about the antibody response of the host as an indicator of the pathogenicity of the infecting hemolytic streptococcus were available.

It is doubtful whether the probably small risk of rheumatic fever and glomerulonephritis in the open civilian population justifies the extensive antibiotic therapeutic recommendations that have been based upon experience in military populations.¹⁶ Moreover, recent papers have stressed the impossibility of defining a streptococcal pharyngitis by clinical examination

alone^{14,17-20}; without bacteriologic control about 40 to 70 per cent of the patients with sore throat who are treated with penicillin will be unnecessarily exposed to the risk of sensitization.

The present study has been undertaken to determine, in a pilot experiment, the possibilities of a controlled study of streptococcal pharyngitis in the open civilian population of a small town under endemic as well as epidemic conditions. The results cover a period of two years, from May, 1959, through April, 1961. In May, 1961, a more extensive survey in 20 general practices was started to establish with more precision the attack rate of rheumatic fever and glomerulonephritis in a larger civilian population group in The Netherlands.

The following points were studied: the frequency of cases of acute pharyngitis (seen by the general practitioner); the incidence of *Streptococcus pyogenes* in these cases; the serologic groups and types of the isolated strains; the antibody response of the host as determined from the acute-phase and convalescent-phase serums of as many patients as possible, irrespective of the results of the bacteriologic examinations; and the incidence|| of rheumatic fever and acute glomerulonephritis as observed in the period of study, regardless of previous indication of tonsillitis.

METHODS

Selection of the Patients and Design of Study

All patients with acute upper respiratory disease who presented themselves to the general practitioner were interviewed and examined.** Admission to the study was limited to patients who fulfilled the following criteria: the presence of a sore throat, especially on swallowing; the presence of redness of the tonsil

||The word "incidence" is used for all cases of rheumatic fever and acute glomerulonephritis seen by the general practitioner during the two-year period.

**More extensive details about the population will be presented in a subsequent paper.²¹

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(or tonsils) or of other lymphoid tissue of the pharynx in the absence of tonsils; the absence of concurrent excessive rhinorrhea; and the absence of concurrent laryngitis, tracheitis or bronchitis.

Since fever was not a prerequisite for admission, we also hoped to include mild cases of "tonsillitis" but to exclude by the third and fourth criteria as much as possible the cases that were most probably of viral origin.

Clinical signs and symptoms were recorded and graded on standardized data cards. The cases qualifying for study according to the criteria were allocated to two treatment groups. The person just entering the study was assigned the foremost card from a file in which color-coded cards had been placed in systematic alternating order. Thus, the color of the card assigned determined the treatment group. A follow-up examination was made ten and thirty days after the initial investigation, and clinical findings were again recorded on the same card. All suggestive signs and symptoms of rheumatic fever and glomerulonephritis were specially noted; all patients with an illness suggestive of rheumatic fever were seen by the Department of Pediatrics or the Department of Microbial Diseases, University Hospital in Leiden, where the criteria of Jones²² were employed to establish the diagnosis. Suppurative complications like otitis media, peritonsillar abscess and scarlet fever were not systematically recorded. The presence or absence of tonsils was not recorded in this study.

The completion rate for the follow-up study of clinical signs in the years 1959, 1960 and 1961 was, respectively, 73, 96 and 100 per cent for two examinations and 59, 92 and 60 per cent for three examinations.

The low completion rate in 1959 was the direct result of the program design. In addition to the notation of local signs of acute pharyngitis, a clinical examination of the heart (including blood pressure) was desired, a search for a rash had to be made, and blood had to be taken for erythrocyte sedimentation rate and determination of antistreptolysin-O titer. This program was impracticable in view of the area resources. It was impossible for the single general practitioner involved to fulfill these requirements during busy office hours or on home calls, and patients were reluctant to co-operate voluntarily in such an extensive study of a relatively mild disease.* The program was therefore reduced in 1960 to the recording of the local signs and symptoms of tonsillitis and the sampling of blood only on the tenth and thirtieth days after the initial visit. The low completion rate in 1961 was directly due to the introduction into the village of a second and associated general practitioner who had to become accustomed to the demands of this study.

*In Holland the general practitioner often has to see 20 to 40 patients at his office and to make 10 to 30 home calls a day, depending on the season.

Children under four years of age were excluded from the study because it is difficult to obtain from this group reliable information about the presence of soreness of the throat on swallowing. Since this age group is not especially prone to rheumatic fever the bias of this shortcoming will be relatively small.

From all patients throat swabs were taken on the first visit and on the tenth and thirtieth days of follow-up study. Dry, untreated cotton-wool swabs were used, and these were sent by mail to the laboratory. It is realized that drying out of the swabs may have interfered with the bacteriologic yield of *Str. pyogenes*; the swabs were in the mail for twenty-four to forty-eight hours. The overall incidence (60 per cent) for Group A streptococci of the initial swabs and some unpublished observations regarding the effect of drying upon the yield of streptococci with the culture methods used suggest that the procedure used does not interfere greatly with the expected results. The completion rate of throat swabbing correlates with that found for the clinical examination and was therefore lower in 1959 and 1961. Blood samples were drawn in the beginning at the same time that clinical signs were noted and throat swabs were taken. However, it soon became apparent that the taking of blood samples at the home of the patient met with some difficulties. From 1960 on, therefore, blood samples were drawn on the tenth and thirtieth days only. The completion rate for the consecutive years was as follows: no blood sample obtained, 33, 9 and 9 per cent; 1 sample obtained, 18, 20 and 30 per cent; 2 consecutive samples obtained, 24, 68 and 57 per cent; 3 consecutive samples obtained, 25, 3 and 4 per cent.

In all patients at least 1 urinalysis was performed, and in most patients 2 determinations were done. Proteinuria was determined by the Albutest method²³ and considered to be significant when more than 1 mg. per milliliter was found. Hematuria was considered to be significantly present when 10 or more red blood cells per high-power field (300X) were seen. The laboratory tests on the urine were done by the general practitioner or his technician.

Distribution of Therapy

The patients were divided by systematic alternate allocation into two groups: those who received antibiotics (penicillin); and those who were treated symptomatically or with sulfonamides. The effect of sulfonamides upon the continuous presence of hemolytic streptococci in the throat is negligible, according to various authors.^{7,24-26} This observation is also supported by the findings of the present study. Those treated symptomatically and with sulfonamides were therefore considered to belong to one group. Penicillin was given orally as penicillin V or by injection as benzathine penicillin G. The advised dose for penicillin V was 125 mg. four times a day, to be given for at least ten days. Benzathine penicillin G was

TABLE 1. Efficacy of Therapy on Eradication of *Str. pyogenes*.

INTERVAL AFTER IN- FECTION	PATIENTS TREATED WITH SULFONAMIDES				PATIENTS TREATED WITH PENICILLIN V*				PATIENTS TREATED WITH BENZATHINE PENICILLIN G			
	SAME TYPE		NEW TYPE		SAME TYPE		NEW TYPE		SAME TYPE		NEW TYPE	
	days	number percent- age	number percent- age	number percent- age	number percent- age	number percent- age	number percent- age	number percent- age	number percent- age	number percent- age	number percent- age	number percent- age
0	56	100	—	—	20	100	—	—	42	100	—	—
10	51	91	1	2	6	30	2	10	1†	2	—	—
30	34	61	1	2	7	35	0	0	1†	2	—	—

*15 patients treated for 5-8 & 5 for 10 days.
†Different patients (5% failure).

given in a dosage of 600,000 units to children under ten years of age and 1,200,000 units to those above ten years of age, as a single intramuscular injection. Sulfonamides were given for a period of five days (3 gm. daily), with no attempt to have a group comparable to the group receiving penicillin by mouth regarding duration of therapy. Acetylsalicylic acid was the most commonly used analgesic. If sucking tablets were administered they were known not to have any bactericidal effect. The physician was permitted to transfer the patient from the symptomatic or sulfonamide group to the penicillin group if complications were present at the first visit, if the patient had a history of rheumatic fever or if there were no changes in the patient's condition after a trial of symptomatic or sulfonamide therapy. The psychologic difficulty of prescribing different therapies for 2 members of the same family, each having the same complaints, also altered the equality of grouping slightly. This problem was recognized in the first study year and was corrected by the introduction of more penicillin cards in the second year of investigation.

In total 115 patients received symptomatic (17 patients) or sulfonamide (98 patients) therapy, and 114 penicillin therapy (41 by mouth and 73 by injection).

A remarkable effect was the spontaneous shift from orally administered penicillin V to benzathine penicillin G in 1960, which was due to the physician's observation of a relatively high number of therapeutic failures in the group treated orally with penicillin.

Laboratory Methods

On arrival at the laboratory the throat swabs were inoculated on the surface of a 5 per cent defibrinated sheep-blood agar plate and were subsequently immersed in a sheep-blood broth. After incubation at 37°C. for eighteen to twenty-four hours the plates were examined for colonies of *Str. pyogenes* and graded according to the yield into four groups: 0-10 colonies, +; 11-20 colonies, ++; 21-50 colonies, +++; and more than 50 colonies, ++++. When the plate was negative, a subculture on a blood-agar plate was made from the blood broth and incubated for the next twenty-four hours. This sheep-blood broth proved to be comparable with a modified fluid, Pike's enrichment medium,²⁷ and represented

a relatively anaerobic medium favorable for isolating streptococci. Representative colonies were subcultured and grouped according to Lancefield's technic.

RESULTS

Prevalence of Pharyngitis

During the two-year period 233 patients were seen. Four cards could not be used for analysis because they did not fulfill the requirements for admission, so that the data are given for 229 cases.

Of the 151 isolated strains of *Str. pyogenes* 138 belonged to Group A (91 per cent), 7 to Group B (5 per cent), 2 to Group C (1 per cent), and 4 to Group G (3 per cent). In 60 per cent of all cases of pharyngitis a Group A streptococcus was isolated. Seventy-three patients with Group A streptococci were treated with some form of penicillin therapy, and 65 received no antibiotics.

The distribution of the types observed during this period is described in the subsequent paper.²¹

Effect of Therapy on Eradication of *Str. pyogenes*

In the group treated with sulfonamides for five days 91 per cent of 56 patients continued to carry the same type of streptococcus for at least ten days, and 61 per cent for at least thirty days (Table 1). This is comparable with the 73 per cent rate of persistent carriers after untreated exudative streptococcal pharyngitis in the Warren Air Force Base study.²⁸

Thirty per cent of the patients treated with penicillin V by mouth harbored the same type of streptococcus after ten days, and 35 per cent after thirty days.* In the benzathine penicillin group these figures were, respectively, 2 and 2 per cent. The differences between the results in the patients treated with sulfonamides and those treated with some form of penicillin are highly significant (p less than 0.0005), as are the differences in eradication rates between the groups receiving penicillin by mouth and benzathine penicillin intramuscularly (0.001 less than p less than 0.005). In 4 cases of the 118 patients sufficiently followed up during a thirty-day period a change of streptococcal type was encountered that gave a change

*It should be noted that most of the patients took their capsules only for five to eight days. From 5 patients taking their penicillin for the full ten only 1 still harbored the same type of streptococcus after ten and thirty days. The rather poor results of oral penicillin therapy may therefore have been due mostly to insufficient duration.

rate of 3.4 per hundred person months, comparable with other studies,¹⁰ and a rate of 0.41 streptococcal acquisitions per person per year. The results with a single injection of benzathine penicillin G are in complete agreement with the reports of other authors,^{8,14} who found that with this therapy more than 90 per cent of the patients were protected from acquiring a new type for at least three weeks.

A similar effect of sulfonamides upon subsequent throat swabs was observed in three studies in Great Britain,^{7,24,26} in which 30 to 60 per cent of the throat swabs were still positive after one to four weeks. The high persistent carrier rate in cases treated with sulfonamides confirms the assumption that these patients can serve as a control group for the attack rate of rheumatic fever and glomerulonephritis.

No correlation between the grade of positivity of the initial swab and the persistence of the carrier rate could be found, but the numbers in each group were too small to be conclusive.

Incidence of Rheumatic Fever and Glomerulonephritis

In the two-year period definite rheumatic fever developed in 4 patients. In 1 other the disease was possibly present. Although all 4 patients acquiring definite rheumatic fever had suffered from an attack of pharyngitis two to three and six weeks previously, they had not called in medical help for their sore throats but had presented themselves primarily with the signs and symptoms of this late complication. These cases would therefore have been missed by any tentative program for prevention of the late sequelae of streptococcal infections. Three of the patients were boys (six, nine and ten years old), and 1 was a married woman, thirty-five years of age, who had had pharyngitis six weeks previously. *Str. pyogenes* could be isolated from the throat swabs of the 3 boys but not from the swab of the female patient, because in her case penicillin treatment was installed before throat swabbing was attempted. All patients showed increased antistreptolysin-O titers.

The possible case developed in a male patient, sixty-three years of age, who had migratory polyarthritides and a rash suggestive of rheumatic fever. However, his throat contained no streptococci that could be isolated; the history was negative for pharyngitis, and no rise in antistreptolysin-O titer could be detected.

In 4 patients (3 female and 1 male) rheumatic complaints developed during the course of the pharyngitis, usually early in the illness (first or second day). None of them fulfilled the Jones criteria for definite rheumatic fever, but 3 of them were seen in December, 1959, with Type 1 pharyngitis, and 1 in December, 1960, with Type 12 pharyngitis. All had significantly raised antistreptolysin-O titers, even up to 5000 units per milliliter. They were twenty-nine years, forty-two years, forty-five years and fifty years of age, so that all were beyond the age limit in which

TABLE 2. *Streptococcal Distribution in Patients with and without Proteinuria.*

DISTRIBUTION OF STREPTOCOCCI	PATIENTS WITHOUT PROTEINURIA*		PATIENTS WITH PROTEINURIA*		TOTAL CASES	PERCENT-AGE
	NUMBER	PERCENT-AGE	NUMBER	PERCENT-AGE		
None	90	42	1	6	91	40
Type 12	24	11	6	38	30	13
Other type	99	47	9	56	108	47
Totals	213		16		229	

*10th-30th day.

rheumatic fever is considered to be predominantly prevalent.

No cases of acute hemorrhagic glomerulonephritis were found, although Type 12 infection caused 22 per cent of the cases of pharyngitis and that type was present throughout the two-year period. One woman, seventy-seven years of age, acquired a transient hematuria on the tenth day of investigation after Type 12 pharyngitis and was treated with penicillin V by mouth for five days. Proteinuria was present in 17 patients at the initial investigation, but it occurred in 9 cases who harbored no streptococci in their throats and in 8 patients with various types of streptococci. These cases of proteinuria must be considered nonspecific. Of the 16 patients (10.9 per cent of all with Group A streptococci) showing proteinuria on the tenth or thirtieth day, or both, only 1 case was in a nonstreptococcal sore throat. Six were preceded by a Type 12 infection (Table 2). The distribution of Type 12 infections in cases with late proteinuria was significantly different (p equal to 0.001) from the overall distribution of this type.

Clinical Features of the Pharyngitis

The prediction of a streptococcal sore throat by clinical judgment alone has been reported to fail in 20 to 30 per cent of the cases.^{14,17-20,29}

The best agreement was found by the authors who included a group of cases with "questionable diagnosis." On the whole, however, about equal percentages of disagreement between the physician's diagnosis and the bacteriologic results were observed. It has recently been pointed out²⁰ that it is clinically impossible to predict a streptococcal sore throat from single local or general signs or symptoms and that the best correlation is found by syndromes of clinical signs as indicators of streptococcal pharyngitis. The syndromes were observed in 36 per cent of all streptococcal cases, so that about 64 per cent will be missed. From the findings of several other authors the same conclusions can be drawn.^{8,14,30-34}

Since the cases in the present study were defined by the fact that soreness on swallowing and redness of the pharynx were obligatory for admission to the study it was impossible to evaluate the clinical data in a similar way. One hundred and eighteen patients

out of the 206 (137 positive for *Str. pyogenes*) who could be analyzed showed exudate as an additional symptom, and in 76 per cent of these, streptococci could be isolated from the initial swab. Seventy per cent of 166 patients who had an anterior cervical adenitis harbored streptococci, and 79 per cent of 103 who showed both signs were positive on bacteriologic examination. These percentages are similar to those found in comparable syndromes.²⁰ When related to the presence of *Str. pyogenes*, 66 per cent of the patients with positive throat swabs had some degree of exudate. In the group with negative throat cultures this symptom was present in 41 per cent, and, although significantly lower (0.001 less than p less than 0.005), it could not be considered to be of much help in establishing a purely clinical diagnosis. There was no difference between the rate of adenitis in the group harboring streptococci and the group with negative cultural findings. Because no correction could be made for the presence or absence of tonsils the results presented here should be regarded with reserve.

During the two years of study a recurrence of the streptococcal infection within one month was seen in 4 patients. Three of these were treated primarily with penicillin V by mouth, and 1 with sulfonamides. In 1 of the former the recurrent infection was the reason for a change to benzathine penicillin G. In 6 other cases the general practitioner changed from sulfonamide therapy to benzathine penicillin G treatment. All changes were based on the fact that the clinical condition of the patient was getting worse during the first ten days (secondary change). One patient on initial investigation suffered from a peritonsillar abscess but was assigned to the penicillin group by the systematic-allocation process. Two patients suffered from a Type 14 scarlet fever and were therefore treated with penicillin (primary change). The low change rate of 4 per cent emphasized the feasibility of a similar study in a larger group of general practitioners.

Estimates for the Prevalence of Streptococcal Pharyngitis and Subsequent Late Sequelae

Accepting that an overall infection rate of 11.2 infections per 100 persons per year, as figured from relevant data from the literature,²¹ is also valid for the population of Voorhout, 1035 infections due to Group A streptococci must have been present in the two years of study. Since only 138 patients with pharyngitis due to Group A streptococci were seen by the physician, probably 897 cases would have been missed by any control program for the prevention of rheumatic fever in the open civilian population. This figure is much higher than that suggested^{35,36} for military populations but similar to those suggested for rural-area populations.³⁴

When the 4 cases of rheumatic fever preceded by the unseen pharyngitis are adjusted to the estimated

number of cases of expected streptococcal pharyngitis the attack rate for rheumatic fever is 0.39 per cent — essentially the same percentage as that found in the control group of Siegel, Johnson and Stollerman.¹⁴ Adjusted to the expected 960 cases of untreated streptococcal pharyngitis, rheumatic fever developed in 0.42 per cent of the patients.

The low attack rate for rheumatic fever in the open civilian population is confirmed by studies^{10,34,37,38} in which streptococcal illnesses were inadequately treated with antibiotics. An attack rate of 2.2 per cent could be calculated for the seven-year study in a Czech village (Zhoř).^{37,38} Of the 4 cases of rheumatic fever, 2 were recurrences; 2 cases were observed in the first study year, and 2 in the seventh study year. When the patients with recurrent rheumatic fever are excluded the attack rate is 1.1 per cent.

This attack rate of 1.1 per cent is essentially the same for some other selected districts of Czechoslovakia, as could be calculated from an average infection rate of 10 streptococcal infections per 100 persons per year and the reported incidence of definite rheumatic fever per 100,000 population.^{35,39} The attack rate varied from 0.16 to 1.1 per cent, with a mean of 0.7 per cent.

As in the study in Voorhout, no cases of acute glomerulonephritis were seen in the seven-year study in the Czech village. On the basis of reported numbers of hospital admissions³⁸ the attack rate for 5 regions of Czechoslovakia could be calculated to be between 0.2 and 0.5 per cent for children and between less than 0.1 and 0.3 per cent for adults. But it is assumed that some of the reported cases would not meet more exact criteria for the diagnosis of acute glomerulonephritis.

In 7 patients rheumatic fever developed during a three-year survey in 2 villages in New York State.¹⁵ Assuming that 70 per cent of the patients with clinical diagnoses of streptococcal illness harbored Group A *Str. pyogenes*, an attack rate of 0.75 per cent can be calculated. Since only 3 of the 7 patients had antecedent pharyngitis the adjusted attack rate after streptococcal pharyngitis was 0.32 per cent. One restriction should be made. All the cases of rheumatic fever were seen in 1 of the 2 villages, and therefore a significant difference existed in attack rate between the 2 study populations (0.025 less than p less than 0.05). Because the 2 groups were about equal in size, the attack rates might have been as high as 1.4 per cent overall, or 0.6 per cent for patients with antecedent pharyngitis.

The overall annual incidence of rheumatic fever in Voorhout was 0.43 per 1000 persons per year and 0.85 per 1000 children per year in the age group under fifteen years. The latter percentage is considerably higher than those reported for England and Wales,⁴⁰ but comparable with that found in the British Army.⁴¹

Marked differences of the incidence of rheumatic fever can be expected to exist between various countries. On the whole, the estimates of the present study for the attack rate of rheumatic fever seem to resemble the figures reported for the United States and for Great Britain more closely than those of mid-European countries such as Czechoslovakia.

DISCUSSION

The data presented in this study are in various ways restricted. The figures obtained are in many ways too small to permit a definite and well founded opinion either on the magnitude of the attack rate of rheumatic fever and acute hemorrhagic glomerulonephritis after untreated streptococcal pharyngitis as it occurs in the open civilian population or on the necessity of penicillin therapy in patients who present themselves to a general practitioner.

The most remarkable result of this pilot study is the fact that none of the 4 patients in whom rheumatic fever is known to have developed after an antecedent pharyngitis consulted their doctors for the symptoms of a sore throat but were first seen when the complaints of rheumatic fever had developed. Therefore, they would all have been missed by any therapeutic program for the prevention of the late sequelae of streptococcal illness.

Since it is likely that these 4 cases originate from considerable numbers with disease due to Group A streptococci not seen by the general practitioner, the number of these patients has been calculated for various supposed attack rates, together with the correspondent infection rate per 100 persons per year and the percentage of patients not sufficiently ill to consult their doctors (Table 3).

In this connection it was necessary to correct the number of patients with a positive throat culture for Group A streptococci who did consult the doctor for possible carriership only.

As shown in the following paper²¹ only 52 per cent of the patients with a positive culture for Group A streptococci and not treated with antibiotics seen in this study showed a significant change in antibody titers. However, even in diseases of certain streptococcal origin, such as scarlet fever, 20 to 30 per cent of the cases will not show a significant increase in

antistreptolysin-O titer; thus, one would come to the conclusion that about 70 per cent of the cases with a positive culture in this study were "proved" cases of streptococcal sore throat.

The various figures resulting from these facts and suppositions do not seem to correlate well with those generally accepted for the various headings today. With a 3 per cent attack rate for rheumatic fever after streptococcal sore throat the resulting infection rate per 100 persons per year is far too low. With a 0.5 per cent attack rate, which brings the infection rate more in accordance with the figures from the literature²¹ on this point, the number of patients not seen by the doctor seems incredibly large (755) and the ratio of these patients to total number of infections incredibly high (89 per cent).

But even if one assumes the attack rate of rheumatic fever after proved streptococcal pharyngitis to be 1 per cent,¹⁴ the number of such infections not seen by the doctor would be 355 during the period of investigation. If one accepts a comparable antibody response in patients with mild or subclinical disease to those with a clinical infection in this study, this would mean that in the population under study about 500 cases of pharyngitis with a positive culture for Group A streptococci occurred in patients who had not called in the help of the physician.

Although these figures and percentages for streptococcal infections not seen by the doctor may seem high it may be mentioned on the other hand that in a recent review¹² 66 per cent of 105 patients suffering from rheumatic fever were not seen by their physicians for the antecedent subclinical pharyngitis. Furthermore, a decrease in severity of streptococcal infections in the general population has been reported by several authors.¹³⁻¹⁵ If this is also true for streptococcal pharyngitis a high percentage of subclinical cases becomes more acceptable. Such a supposition is supported by the preliminary data from a much larger study started in May, 1961, on the same general line with the co-operation of approximately 15 general practitioners.

In the first 422 cases fulfilling the criteria of the present study 200 patients had positive cultures for Group A *Str. pyogenes*, and 100, or 50 per cent, were given sulfonamides or symptomatic treatment.

TABLE 3. Relation between Supposed Attack Rates of Rheumatic Fever and Number of Patients with Minimal Symptoms of Proved Acute Streptococcal Pharyngitis that Should Have Occurred in the Population of Voorhout to Give 4 Cases of Rheumatic Fever.

SUPPOSED ATTACK RATE OF RHEUMATIC FEVER	PATIENTS WITH INFECTION DUE TO GROUP A STREPTOCOCCI NECESSARILY PRESENT	PATIENTS SEEN BY DOCTOR & NOT TREATED WITH ANTIBIOTICS*	PATIENTS NOT SEEN BY DOCTOR	PATIENTS SEEN BY DOCTOR & TREATED WITH ANTIBIOTICS†	TOTAL STREPTOCOCCAL INFECTIONS PRESENT	INFECTION RATE/100 PERSONS/YR.	PERCENTAGE OF PATIENTS NOT SEEN BY DOCTOR
%							
3.0	133	45	88	51	184	2.0	48
1.0	400	45	355	51	451	4.8	79
0.5	800	45	755	51	851	9.0	89

*70% of 65 patients with positive culture seen by doctor & not treated with antibiotics.
†70% of 73 patients with positive culture seen by doctor & treated with penicillin.

These 100 patients, representing probably 70 cases of proved streptococcal sore throat, were not followed by any case of rheumatic fever. Again, there were in the population 3 patients with rheumatic fever who had not had pharyngitis clinically important enough to cause them to consult their physicians. Including the previous 4 cases, the total number of cases of rheumatic fever developing with seemingly insufficient warning is 7, against no case of rheumatic fever in 165 "untreated" patients who harbored streptococci of Group A, representing at least 110 cases (70 per cent of 165) of overt, clinically proved streptococcal pharyngitis. Regardless of the number of patients from which these 7 cases of rheumatic fever originate, there is a significant difference (0.025 less than p less than 0.05) between the population that consulted the doctor and the population in which rheumatic fever occurred. This suggests either that the number of subclinical cases is much larger than the number of overt clinical cases or that the difference might be due to some effect of therapeutic attacks since the larger part of the 165 patients were treated by sulfonamides.

The figures in this pilot study are far too small for any but preliminary conclusions about the necessity of penicillin therapy of the patients with acute pharyngitis who consult their physicians. Although penicillin therapy has no toxic side effect the possibility of sensitization is a disadvantage. Because it is impossible to diagnose a streptococcal sore throat with certainty on the clinical symptoms alone and because it is not possible in the Netherlands to perform cultures in all cases of pharyngitis, at least 60 per cent of all patients would receive penicillin unnecessarily.

The 1 to 2 per cent risk of sensitization to penicillin in the other 40 per cent of the patients who do have a proved streptococcal sore throat seems to be amply justified in the face of a 3 per cent risk of rheumatic fever, provided the latter figure is valid for the frequency of late sequelae in the general population.

Other authors and the data in this study have raised considerable doubt about the validity of the 3 per cent attack rate of rheumatic fever after streptococcal pharyngitis. The fact that all the patients observed to be suffering from rheumatic fever were outside the controlled therapeutic program may lead to the paradox that it is not the patients with streptococcal sore throat consulting their physician who should be treated but the much larger subclinical or nearly subclinical group who, by being subclinical, escape the attention of the physician. This would force one to reconsider the advisability of giving penicillin to every patient who comes to the office with complaints of a sore throat. Here is a problem of competing risks: the risk of rheumatic fever as against the risk of penicillin sensitization.

SUMMARY AND CONCLUSIONS

During a two-year period of investigation in a village in the western part of the Netherlands, 229 patients consulted their general practitioners for complaints of an acute pharyngitis. One hundred and thirty-eight patients (60 per cent) harbored Group A *Streptococcus pyogenes* in their throats. Virtually all strains could be typed serologically. Seventy-three patients with positive throat cultures were treated with either penicillin V by mouth or a single intramuscular injection of benzathine penicillin G. The remaining 65 were treated with sulfonamides or analgesics. None of the 65 control patients contracted rheumatic fever, but 4 cases of rheumatic fever preceded by a subclinical pharyngitis occurred in the remaining population not seen by physicians. Because these 4 patients did not consult their physicians for the symptom of sore throat they were not prevented from acquiring rheumatic fever. No cases of definite acute glomerulonephritis were observed although 16 patients (11 per cent of all streptococcal cases) showed proteinuria on the tenth or thirtieth day of follow-up study. Six of these late but transient proteinurias were preceded by a Type 12 infection. Only 1 case of a transient hematuria was seen; this case was also preceded by a Type 12 infection.

As in other studies, it was not possible to diagnose a streptococcal infection on the basis of clinical symptoms or signs alone.

The results indicate that a considerable number of patients were not attended by their physician, suggesting that they did not consider the (streptococcal) pharyngitis of enough importance to seek medical care. They would have been missed by any therapeutic program for the prevention of rheumatic heart disease.

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ATTACK RATE OF STREPTOCOCCAL PHARYNGITIS, RHEUMATIC FEVER AND GLOMERULONEPHRITIS IN THE GENERAL POPULATION*

II. The Epidemiology of Streptococcal Pharyngitis in One Village during a Two-Year Period

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ALTHOUGH in the past twenty years the epidemiology of streptococcal infections has been studied extensively, only a few studies were conducted in the open civilian population. Most were done in more or less closed communities,^{1,2} in selected families^{3,4} or with children.⁵⁻⁸ In only one study was the population of a complete village followed clinically,

bacteriologically and serologically⁹ during a period of seven years.

The results of the attack rate of rheumatic fever and acute hemorrhagic glomerulonephritis in the population of a small town during a two-year period (May, 1959, through April, 1961) were presented in a preceding report.¹⁰ In this paper the epidemiology of acute pharyngitis as seen by the general physician of this village is presented.

METHODS

The definition of acute pharyngitis and the requirements that the patients had to fulfill to be admitted to the study are given in the preceding paper.¹⁰

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