Prevention of Rheumatic Fever

Treatment of the Preceding Streptococcal Infection

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The prevention of acute rheumatic fever by the prompt treatment of streptococcal infections with penicillin has been attempted in this study. The results obtained show that this attempt was successful, and, because of their importance, these results are presented here in a preliminary report.

The significance of an adequate means of prevention may be realized when it is considered that rheumatic fever develops in an estimated 200,000 to 250,000 persons in the general population of the United States yearly.1 Figures for the Armed Services similarly show a high incidence, with an average of 7,300 cases annually for the seven year period from 1942 through 1948.2 The gravity of the disease itself is emphasized by the estimate of Paul that at least 460,000 persons in the country today have rheumatic heart disease.3 Not only is rheumatic fever a menace to health, but it is also a serious economic problem. A conservative estimate of the cost of each case that occurs in the Armed Services is $16,000.4

Description of the Study

The study was conducted at Fort Francis E. Warren, in southeastern Wyoming. The Fort is an air force technical training base where approximately 80 per cent of the men are trainees who report after twelve weeks of basic training at a southwestern base. The study began Jan. 24, 1949, and ran continuously until July 1, 1949, except for a ten day period in April. Although the average strength of the base during the study was 8,000 men, the actual number exposed to infection was much greater because the men remained in school only eight to thirty-two weeks.

All patients admitted to the hospital for disease of the respiratory tract were seen within a few hours by one of the members of the professional staff of the laboratory. Those having exudate on the tonsils or on the pharyngeal wall were included in the study group. A total of 1,634 such patients were observed.

A total of 798 patients whose Air Force serial numbers ended in an even digit received penicillin treatment, and 804 patients whose serial numbers ended with an odd digit comprised the control group and received no specific treatment.6 Prior to March 3, 1949 the treatment consisted of 300,000 units of crystalline procaine penicillin G (suspended in peanut oil containing 2 per cent aluminum monostearate) given intramuscularly as soon after admission as possible. This dose was repeated in seventy-two hours. After March 3 the following change was made in the dosage schedule: 300,000 units were administered at the time of admission and again in forty-eight hours, and 600,000 units were given ninety-six hours after the initial dose. Of the 798 patients who received penicillin, 253 were treated before March 3. Eighty-eight per cent of the treated patients received the first penicillin within sixty hours after the onset of the symptoms of the streptococcal illness.

Follow-up studies for the detection of rheumatic fever were performed between the third and fourth weeks after the initial infection, without knowledge of the serial numbers of the patients or of their previous treatment. Those patients suspected of having acute rheumatic fever were hospitalized until a satisfactory diagnosis was established. Rigid criteria for diagnosis were followed. A modification of the classification of Jones8 was used. This classification may be seen in the following tabulation:

Major Manifestations

Carditis
a. Definite cardiac enlargement
b. Appearance of a significant murmur before not present
c. Friction rub
d. Heart block or other electrocardiographic findings indicative of carditis
e. Cardiac failure

Migrating polyarthritis

History of recurrences

Chorea

Subcutaneous nodules

4. Thirty-two patients were excluded from the analysis because they were treated with aqueous penicillin by the ward physician for various reasons. In none of these patients did acute rheumatic fever subsequently develop.

MINOR MANIFESTATIONS

Fever
Abdominal pain
Arthralgia
Skin rash
a. Erythema marginatum
b. Erythema multiforme
Epistaxis
Pulmonary changes
Non-specific electrocardiographic changes
Elevated erythrocyte sedimentation rate (20 or above considered abnormal)
Anemia

Pulmonary changes and anemia were encountered but did not contribute to the classification of these patients. No patient with chorea or subcutaneous nodules was encountered. Only persons in whom acute rheumatic fever developed between ten to thirty-five days after the onset of the observed streptococcal infection are included in this report.

Throat cultures and blood specimens were obtained from the patients on admission and again at the time of the follow-up examination. Strains of beta hemolytic streptococci isolated from cultures were grouped and typed according to the method of Lancefield.8 Anti-streptolysin O titration was performed on acute and convalescent sera according to a modification of the method of Hodge and Swift.7

RESULTS

Of the 798 patients that were treated with penicillin, definite acute rheumatic fever developed in only 2. In contrast, the disease developed in 17 of the untreated patients (table 1), a difference which could be due to chance only 6 times in 10,000. Of the 2 patients in the treated group who became ill with rheumatic fever, 1 was treated within eight hours after the onset of the symptoms of streptococcal disease and the second approximately seventy-two hours after the onset.

Probable acute rheumatic fever developed in 2 patients in the treated group and in 6 patients in the untreated group. Of the 2 patients in the treated group, I received penicillin forty-eight hours after the onset of symptoms of streptococcal disease and the second one hundred and eight hours after the onset. Whether the time of treatment of the initial infection is related to the development of poststreptococcal non-suppurative complications cannot be determined at this time.

The effect of penicillin treatment on the presence of beta-hemolytic streptococci in cultures of the throat is shown in table 2. In the treated group the number of persons having streptococci was reduced from 78.3 per cent on admission to 18.1 per cent at the time of the follow-up examination. The untreated group showed a reduction from 81.7 per cent to only 52.7 per cent.

The development of antistreptolysin O in the treated and untreated groups was also different. In the treated group only 51 per cent of the patients showed a rise in titer of two or more tubes, while 73 per cent of the untreated patients showed a similar rise. Tests of significance support the validity of these differences.

The prevention of rheumatic fever, the inhibition of antibody and the partial eradication of streptococci in the group of patients treated with penicillin assume more significance when the composition of the treated group and that of the control group are compared. That the two groups were comparable is demonstrated in table 3, in which various features are presented. Moreover, a large proportion of the illnesses in both groups were streptococcal in origin, since group A beta hemolytic streptococci were isolated from 80 per cent of all cultures made at admission and since 73 per cent of the untreated patients showed an antistreptolysin response of two or more tubes.

COMMENT

The data presented concerning the incidence of rheumatic fever in the treated and control groups establish the fact that penicillin therapy of acute streptococcal infections will almost completely prevent the subsequent occurrence of rheumatic fever. These results emphasize again the close relationship between streptococcal disease and rheumatic fever.

Attempts to prevent the occurrence or the recurrence of rheumatic fever during the last decade have centered around the streptococcal disease that precedes most cases of acute rheumatic fever. Coburn,6 Kuttner and Raynchabah3 and Hodges10 showed that sulfonamide drugs, given prophylactically, not only reduced the incidence of streptococcal disease but also reduced the occurrence of rheumatic fever. This would seem to be a practical means of prevention in two situations: (a) in closed groups in which the incidence of streptococcal disease is extremely high and (b) in select groups, such as patients with inactive rheumatic fever or rheumatic heart disease, in which the danger of recurrence is great.

This method of prevention has not proved to be practical for the general population, however, because of the toxicity of the sulfonamide drugs, the high percentage of sulfonamide-resistant strains of streptococci that develop and the difficulty that is entailed in mass prophylaxis.11

Treatment after the development of the streptococcal infection has been another approach to the problem. Sulfonamide drugs have proved to be ineffective when used in this manner.11 Experience with penicillin has been conflicting. Weinstein, Bachrach and Perrin12 treated 225 patients with streptococcal disease with penicillin; in 7 of these patients rheumatic fever subsequently developed. This observation supports Finland’s11 conclusion, from a review of the literature, that penicillin is not effective when used in this manner for the prevention of rheumatic fever. On the contrary, Massell, Dow and Jones14 employed penicillin to treat ten clinical and five subclinical hemolytic streptococcal infections in patients hospitalized for rheumatic fever or rheumatic heart disease; the patients failed to exhibit subsequent recurrences. Jersild19 has shown that poststreptococcal complications, including nephritis, are reduced after penicillin treatment of the initial illness, but he makes no statement about the occurrence of rheumatic fever.

The theory has been advanced that rheumatic fever is associated with a peculiar response to an unknown antigen-antibody reaction. Kilbourne and Loge16 showed that early and intensive penicillin therapy against streptococcal disease suppressed the production of anti-streptolysin O. It has been shown here that adequate treatment with penicillin not only suppresses the anti-streptolysin response but also prevents rheumatic fever. Whether the antibody suppression is only a reflection of the inhibition of some more basic process in the mechanism of rheumatic fever or is in itself the responsible factor is entirely speculative at this time.

| TABLE 3—Comparability of Treated and Untreated Groups |
|---------------------------------|-------|-------|
|                                 | 798   | 804   |
|                                 | Treated Patients | Untreated Patients |
| Age (years):                    | (Percentage) | (Percentage) |
| 17-19                           | 61.0   | 62.0  |
| 20 and over                     | 39.0   | 38.0  |
| Previous history of rheumatic fever | 3.5   | 4.4   |
| Tonsils present                 | 72.7   | 70.7  |
| Cervical nodes enlarged or tender | 50.1   | 46.3  |
| Leucocyte count 13,000 or over at admission | 44.7 | 56.3 |
| Persons with group A beta hemolytic streptococci at admission | 73.1 | 81.7 |
| Antistreptolysin O titer of 150 units or less at admission | 79.3 | 80.1 |
| Follow-up obtained              | 80.7   | 82.8  |

Evidence is presented to indicate that rheumatic fever can be prevented by the treatment of streptococcal disease with penicillin. A total of 798 patients with streptococcal infections were treated with penicillin; in only 2 did acute rheumatic fever subsequently develop. Of 804 untreated patients, the disease developed in 17. Penicillin therapy likewise suppresses the antistreptolysin O response and eradicates the streptococci in many cases.

Summary

Evidence is presented to indicate that rheumatic fever can be prevented by the treatment of streptococcal disease with penicillin. A total of 798 patients with streptococcal infections were treated with penicillin; in only 2 did acute rheumatic fever subsequently develop. Of 804 untreated patients, the disease developed in 17. Penicillin therapy likewise suppresses the antistreptolysin O response and eradicates the streptococci in many cases.


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