The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

VOL. 143, NO. 2 — CHICAGO, ILLINOIS — MAY 13, 1950

COPYRIGHT, 1950, BY AMERICAN MEDICAL ASSOCIATION

PREVENTION OF RHEUMATIC FEVER

Treatment of the Preceding Streptococcic Infection

CAPT. FLOYD W. DENNY
CAPT. LEWIS W. WANNAMAKER
CAPT. WILLIAM R. BRINK
Medical Corps, Army of the United States
CHARLES H. RAMMELKAMP Jr., M.D.
Cleveland
and
EDWARD A. CUSTER, M.D.
Palo Alto, Calif.

The prevention of acute rheumatic fever by the prompt treatment of streptococcic 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.[2]

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.[4] 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 streptococcic 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 Jones[5] was used. This classification may be seen in the following tabulation:

MAJOR MANIFESTATIONS

- Carditis
  - a. Definite cardiac enlargement
  - b. Appearance of a significant murmur heretofore 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

This investigation was supported through the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, Office of the Surgeon General, Washington, D. C.

From the Streptococcal Disease Laboratory, Fort Francis E. Warren, Wyo., and the Department of Preventive Medicine, Western Reserve University School of Medicine, Cleveland.

1. Swift, H. F.: Rheumatic Fever, in Cecil, R. L.: A Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1947, p. 168.
2. Department of Preventive Medicine, Surgeon General's Office.
3. Paul, J. R.: The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects, New York, Metropolitan Life Insurance Company, 1943.
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.
5. Jones, T. D.: The Diagnosis of Rheumatic Fever, J.A.M.A. **126**: 481 (Oct. 21) 1944.

MINOR MANIFESTATIONS

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

For a diagnosis of definite acute rheumatic fever a patient had to have two major manifestations or one major and two minor manifestations. For a diagnosis of probable acute rheumatic fever a patient had to have one major and one minor, one major or two minor manifestations. Instances of abdominal pain, epistaxis, 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 streptococcic infection are included in this report.

TABLE 1.—*Cases of Rheumatic Fever Found at the Follow-Up Examination in the Treated and Untreated Groups*

	Number of Patients	
	Treated	Untreated
Definite rheumatic fever	2	17*
Probable rheumatic fever	2	6
Total	4	23†

* Test of significance shows that probability is 0.0006.
† Test of significance shows that probability is 0.0002.

TABLE 2.—*Persistence of Group A Beta Hemolytic Streptococci in the Treated and Untreated Groups*

	Treated (Percentage)	Untreated (Percentage)
Persons with group A beta hemolytic streptococci on admission	78.3	81.7
Persons with group A beta hemolytic streptococci on follow-up examination	18.1	52.7

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.[6] Antistreptolysin O titration was performed on acute and convalescent serums 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 streptococcic 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, 1 received penicillin forty-eight hours after the onset of symptoms of streptococcic 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 poststreptococcic nonsuppurative complications cannot be determined at this time.

The effect of penicillin treatment on the presence of betahemolytic 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 streptococcic 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 streptococcic infections will almost completely prevent the subsequent occurrence of rheumatic fever. These results emphasize again the close relationship between streptococcic disease and rheumatic fever.

Attempts to prevent the occurrence or the recurrence of rheumatic fever during the last decade have centered around the streptococcic disease that precedes most cases of acute rheumatic fever. Coburn,[8] Kuttner and Reyersbach[9] and Hodges[10] showed that sulfonamide drugs, given prophylactically, not only reduced the incidence of streptococcic 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 streptococcic 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.

6. Swift, H. F.; Wilson, A. T., and Lancefield, R. C.: Typing Group A Hemolytic Streptococci by M Precipitin Reactions in Capillary Pipettes, J. Exper. Med. **78**: 127 (Aug.) 1943.

7. Hodge, B. E., and Swift, H. F.: Varying Hemolytic and Constant Combining Capacity of Streptolysins: Influence on Testing for Antistreptolysins, J. Exper. Med. **58**: 277 (Sept.) 1933.

8. Coburn, A. F.: The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy, J.A.M.A. **126**: 88 (Sept. 9) 1944.

9. Kuttner, A. G., and Reyersbach, G.: The Prevention of Streptococcal Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide, J. Clin. Investigation **22**: 77 (Jan.) 1943.

10. Hodges, R. G.: The Use of Sulfadiazine As a Prophylactic Against Respiratory Disease, New England J. Med. **231**: 817 (Dec. 21) 1944.

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 precentage of sulfonamide-resistant strains of streptococci that develop and the difficulty that is entailed in mass prophylaxis.[8]

Treatment after the development of the streptococcic 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 Perrin[12] treated 225 patients with streptococcic disease with penicillin; in 7 of these patients rheumatic fever subsequently developed. This observation supports Finland's[13] 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 Jones[14] employed penicillin to treat ten clinical and five subclinical hemolytic streptococcic infections in patients hospitalized for rheumatic fever or rheumatic heart disease; the patients failed to exhibit subsequent recurrences. Jersild[15] has shown that poststreptococcic complications, including nephritis, are reduced after penicillin treatment of the initial illness, but he makes no statement about the occurrence of rheumatic fever.

TABLE 3.—*Comparability of Treated and Untreated Groups*

	798 Treated Patients (Percentage)	804 Untreated Patients (Percentage)
Age (years):		
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	54.7	56.3
Persons with group A beta hemolytic streptococci at admission	78.3	81.7
Antistreptolysin O titer of 125 units or less at admission	70.3	69.1
Follow-up obtained	80.7	82.8

The theory has been advanced that rheumatic fever is associated with a peculiar response to an unknown antigen-antibody reaction. Kilbourne and Loge[16] showed that early and intensive pencillin therapy against streptococcic disease suppressed the production of antistreptolysin O. It has been shown here that adequate treatment with penicillin not only suppresses the antistreptolysin 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.

Exudate on the tonsils or oropharynx was used as the sole means of selection of patients to be included in this study because it was a rapid, easily standardized method. It was thought that such a criterion would include the majority of streptococcic infections of the respiratory tract, since various studies have shown that exudative lesions of the throat appear in 60 to 90 per cent of streptococcic infections,[17] particularly in a population experiencing epidemic rates of streptococcic illnesses. The isolation of group A streptococci from 80 per cent of the patients and the demonstration of an increase in the antistreptolysin O titer in 73 per cent of the control group indicate that the majority of the patients actually had streptococcic disease. A few undoubtedly had nonstreptococcic exudative tonsillitis.

If the incidence of rheumatic fever is to be reduced materially by early treatment with penicillin, it becomes necessary that streptococcic infections be diagnosed accurately and early. In some cases the clinical findings alone will permit an almost certain diagnosis of streptococcic infection. Characteristically, such illnesses present a sudden onset of sore throat with pain on swallowing, fever and other constitutional reactions, diffuse redness and edema of the soft palate, tonsils and oropharynx, discrete or confluent exudate and large or tender cervical lymph nodes. Supportive data may be obtained from the laboratory. Many patients will have an elevated total leukocyte count. Cultures of the pharynx will almost always show a predominant growth of beta hemolytic streptococci. Depending on the availability and use of the preceding criteria, a large percentage of streptococcic respiratory infections can be reliably and rapidly diagnosed, particularly during an epidemic period. Treatment with penicillin can thus be instituted immediately.

SUMMARY

Evidence is presented to indicate that rheumatic fever can be prevented by the treatment of streptococcic disease with penicillin. A total of 798 patients with streptococcic 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.

11. Commission on Acute Respiratory Diseases: A Study of a Food-Borne Epidemic of Tonsillitis and Pharyngitis Due to Beta-Hemolytic Streptococcus, Type 5, Bull. Johns Hopkins Hosp. **77**: 143 (Sept.) 1945.
12. Weinstein, L.; Bachrach, L., and Perrin, T. S.: Studies of the Influence of Penicillin on the Immune Reactions in Streptococcal Pharyngitis, J. Clin. Investigation **28**: 817 (July) 1949.
13. Finland, M.: Use of Penicillin in Infections Other Than Bacterial Endocarditis, Advances Int. Med. **2**: 350, 1947.
14. Massell, B. F.; Dow, J. W., and Jones, T. D.: Orally Administered Penicillin in Patients with Rheumatic Fever, J.A.M.A. **138**: 1030 (Dec. 4) 1948.
15. Jersild, T.: Penicillin Therapy in Scarlet Fever and Complicating Otitis, Lancet **1**: 671 (May 1) 1948.
16. Kilbourne, E. D., and Loge, J. P.: The Comparative Effects of Continuous and Intermittent Penicillin Therapy on the Formation of Antistreptolysin in Hemolytic Streptococcal Pharyngitis, J. Clin. Investigation **27**: 418 (July) 1948.
17. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic and Nonstreptococcic Diseases of the Respiratory Tract, Arch. Int. Med. **78**: 369 (Oct.) 1946. Footnote 11.

Patents, Commissions, Rebates and Secret Remedies.—An ethical physician will not receive remuneration from patents on or the sale of surgical instruments, appliances and medicines, nor profit from a copyright on methods or procedures. The receipt of remuneration from patents or copyrights tempts the owners thereof to retard or inhibit research or to restrict the benefits derivable therefrom to patients, the public or the medical profession. The acceptance of rebates on prescriptions or appliances, or of commissions from attendants who aid in the care of patients, is unethical. An ethical physician does not engage in barter or trade in the appliances, devices or remedies prescribed for patients, but limits the sources of his professional income to professional services rendered the patient. He should receive his remuneration for professional services rendered only in the amount of his fee specifically announced to his patient at the time the service is rendered or in the form of a subsequent statement, and he should not accept additional compensation secretly or openly, directly or indirectly, from any other source.

The prescription or dispensing by a physician of secret medicines or other secret remedial agents, of which he does not know the composition, or the manufacture or promotion of their use is unethical.—Section 6, Chapter I of the PRINCIPLES OF MEDICAL ETHICS of the American Medical Association.