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**THE LATENT PERIOD BEFORE THE ONSET OF  
ACUTE RHEUMATIC FEVER†**

**INTRODUCTION**

John R. Paul has been interested in the latent period and the incubation period of a variety of infectious diseases because careful study of the host during these periods frequently yields important clues concerning pathogenesis. In the case of rheumatic fever, the latent period begins at the onset of symptoms of the acute group A streptococcal respiratory infection and ends at the time of development of symptoms of acute rheumatic fever. Thus, in the early phase of the latent period, the patient exhibits signs and symptoms of tonsillitis or pharyngitis, whereas in the second phase, unless a suppurative complication supervenes, the patient is asymptomatic.<sup>1</sup>

The occurrence of a latent period prior to the development of symptoms of acute rheumatic fever or acute glomerulonephritis is responsible for the suggestion that these two complications of group A streptococcal infections represent some form of altered tissue reactivity of an immunological nature.<sup>2,3</sup> Ranz, Boisvert, and Spink<sup>4</sup> studied a group of patients during the latent period and suggested, on the basis of bacteriologic studies, that reinfection with a new type of streptococcus may be necessary for the development of these non-suppurative complications. In order to define the normal latent period as well as to determine the effect of reinfection during this time interval the experience at the Streptococcal Disease Laboratory was reviewed. At this facility, all patients with clinically evident streptococcal disease or acute rheumatic fever were hospitalized and studied by standard methods including bacteriologic and serologic techniques.

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Thus, it was possible to define the latent period and to examine some of the factors which might be expected to alter its length.

#### METHODS

The records of all airmen admitted to the hospital at Francis E. Warren Air Force Base between January 1949 and June 1953 with symptoms of acute rheumatic fever were studied. A final diagnosis of acute rheumatic fever was made utilizing the criteria of Jones<sup>6</sup> with slight modification.<sup>8</sup>

During the same period that the patients with acute rheumatic fever were observed, all airmen with symptoms of an acute respiratory illness associated with either fever or exudative tonsillitis or pharyngitis were admitted to a special study unit. After a history, physical examination, oropharyngeal culture and an acute phase serum specimen were obtained, half of the patients received therapy with an antibiotic and the remaining patients were given symptomatic therapy and served as controls. These

TABLE 1. PATIENTS WITH ACUTE RHEUMATIC FEVER INCLUDED IN STUDY

<i>Category</i>	<i>Number</i>	<i>Per cent</i>
Acute rheumatic fever	565	100
Observed during preceding infection	274	48
Date of onset of rheumatic fever not known	23	4
Total analyzed	251	44

studies were designed to determine the effectiveness of various therapeutic regimens in the prevention of acute rheumatic fever. As a part of these investigations each patient was carefully observed during convalescence to determine whether complications developed. A second culture of the oropharynx and a specimen of serum were obtained approximately three weeks after the onset of the streptococcal illness. If the patient developed rheumatic fever, additional cultures were taken. In each case an effort was made to date accurately the onset of symptoms of the streptococcal infection and the time the first rheumatic symptoms appeared. The period between these two events was calculated to the nearest day.

The oropharyngeal swabs were rubbed on sheep blood agar plates and after 18-24 hours incubation *beta* hemolytic colonies were isolated in pure culture. Classification of these cultures into serologic groups and types was performed by standard procedures.<sup>7</sup> Antistreptolysin O titers were determined at the same time on all sera collected from any one patient.

#### RESULTS

During the period of this study 565 patients exhibiting the classical features of acute rheumatic fever were observed on the hospital wards (Table 1). Of these patients, 274 or 48 per cent had been hospitalized previously because of an acute respiratory illness. Examination of these

274 records showed that in 23 the dates of onset of the symptoms of acute rheumatic fever were uncertain, so that the present analysis was limited to the remaining 251 patients.

Table 2 presents the latent periods of these 251 patients grouped in intervals of three days. Since prior studies had demonstrated that indi-

TABLE 2. THE LATENT PERIOD OF 251 PATIENTS WITH RHEUMATIC FEVER OBSERVED DURING A PRECEDING RESPIRATORY INFECTION

Latent period (days)	Initial culture			Negative*	Totals
	Group A streptococcus				
	Single infection†	Two infections‡	Received therapy		
0-2	2	0	5	6	13
3-5	3	0	2	0	5
6-8	6	0	4	1	11
9-11	10	1	2	1	14
12-14	16	1	2	3	22
15-17	11	1	4	4	20
18-20	18	2	2	3	25
21-23	15	2	3	1	21
24-26	17	4	2	4	27
27-29	6	3	2	4	15
30-32	5	2	1	1	9
33-35	4	1	1	2	8
36-45	11	15	6	10	42
Over 45	3	6	6	4	19
Totals	127	38	42	44	251

† Convalescent culture was negative or showed the same type isolated on initial culture.

‡ A type different than that isolated on the initial culture was identified during convalescence. Nine of these patients received antibiotics of whom 7 exhibited an interval of over 35 days.

\* Eighteen of these patients subsequently showed a positive culture.

viduals exhibiting long latent periods usually had experienced an intervening streptococcal infection as determined by bacteriologic, serologic or historical evidence<sup>8</sup> such patients were listed together. Of the entire group of 251 patients 61 or 24 per cent showed latent periods of over 35 days, and 19 or 8 per cent of the intervals were over 45 days. Based on bacteriologic studies alone, 21 of these 61 patients with long latent periods experienced a reinfection, whereas reinfections were demonstrated

in only 17 of the 190 patients with latent periods of less than 36 days. In addition, 26 of the patients with long latent periods either showed no group A streptococci on admission to the hospital for the observed respiratory illness or they received therapy with an antibiotic. In both instances, it appeared reasonable to assume that either an inapparent or a continuing infection with a group A streptococcus probably occurred after the observed illness and before the onset of rheumatic fever.<sup>9</sup> For these reasons it appeared unlikely that most of the cases of acute rheumatic fever with latent periods of over 35 days were directly precipitated by the observed respiratory illness.

TABLE 3. CHARACTERISTICS OF THE PRECEDING RESPIRATORY ILLNESS IN 127 PATIENTS WHO RECEIVED NO SPECIFIC THERAPY AND WHO SHOWED NO BACTERIOLOGIC EVIDENCE OF REINFECTION PRIOR TO ONSET OF RHEUMATIC FEVER

	<i>Number</i>		<i>Per cent present</i>
	<i>Observed</i>	<i>Present</i>	
Exudate	127	98	78
Increase in antistreptolysin titer	118	109	92
Leukocytosis of 12,000 or greater	119	109	92

Since these studies were conducted in a population experiencing epidemics of streptococcal and non-streptococcal respiratory diseases, it was essential to establish the etiology of the observed respiratory illnesses. In addition, it was assumed that specific antistreptococcal therapy of the observed illness or the occurrence of a new, inapparent, streptococcal infection prior to the onset of rheumatic symptoms might affect the length of the latent period. Thus, the 251 patients selected for analysis were subdivided into the various groups presented in Table 2.

There were 127 patients who showed group A streptococci from the culture obtained on hospitalization, who received no specific therapy with antibiotics or sulfonamide drugs, and whose convalescent cultures were either negative or showed the infetcing type of streptococcus. The data presented in Table 3 document the fact that the observed respiratory illnesses in these patients were caused by the streptococcus. The majority of the patients was found to have an exudative lesion of the pharynx or tonsils and elevation of the total leukocyte count. As many as 92 per cent exhibited a significant increase in the titer of antistreptolysin during convalescence.

The distribution of the latent periods observed in these 127 patients is shown in Figure 1 as well as in Table 2. In this group the latent period was greater than 35 days in only 14 or 11 per cent. In 3 patients the latent period was over 45 days. Although bacteriologic evidence of reinfection was lacking in these 14 patients, it seems probable that most had experienced a new, unobserved infection which was not detected by the bacteriologic technique employed. In contrast, the majority of the re-

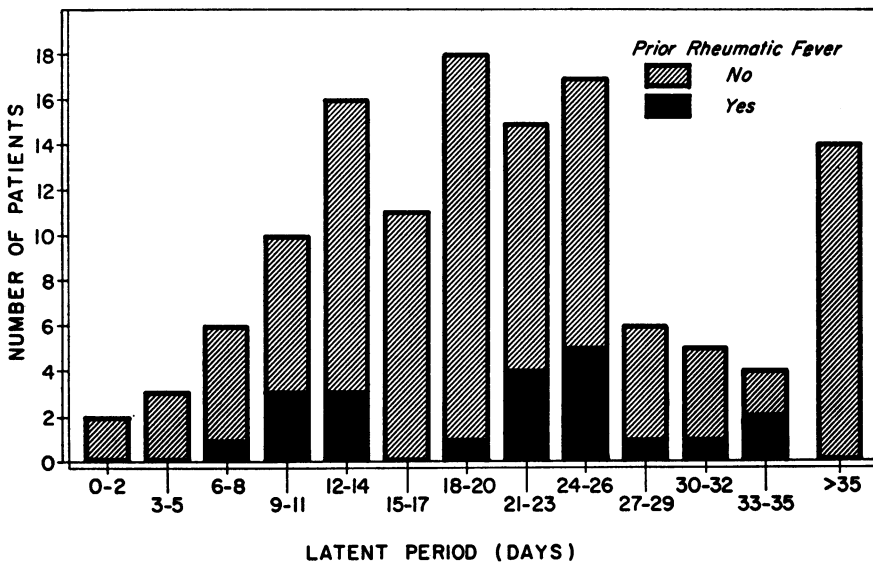


FIG. 1. The latent period in acute rheumatic fever.

maining 113 observed illnesses probably represent infection by a single serologic type.

The mean interval for those patients exhibiting a latent period of less than 36 days was 18.6 days; the median was 19 days. The frequency distribution of the latent periods roughly parallels a normal distribution curve. This is especially true if those patients who have experienced a prior attack of rheumatic fever, as depicted in Figure 1, are eliminated from consideration. The 21 individuals who were experiencing a recurrent attack of rheumatic fever did not exhibit a shortened latent period, nor did any show a latent period of over 35 days.

Of the 113 patients with latent periods of less than 36 days, 11 or 10 per cent, developed rheumatic symptoms during the first 8 days. There were 2 patients whose symptoms of acute rheumatic fever appeared to

develop near the time of onset of the acute respiratory illness. In one the initial antistreptolysin titer was 500 indicating that this patient had recently experienced another streptococcal infection which may have accounted for the apparent short latent period. However, he had no recollection of a recent sore throat prior to the observed illness and examination showed no exudate on the tonsils or pharynx. It is possible that the symptom, sore throat, was associated with the onset of acute rheumatic

TABLE 4. AVERAGE LATENT PERIOD ACCORDING TO THE TYPE OF GROUP A STREPTOCOCCUS CAUSING THE INFECTION

<i>Type of streptococcus</i>	<i>Average interval (days)</i>	<i>Number of patients*</i>
14	19	52
5	20	19
30	17	10
19	17	8
24	15	6
18	21	5
NT	22	5
1	13	3
3	12	3
6	21	1
4	24	1

\* Limited to the 113 patients who received no therapy and showed no evidence of reinfection. The 14 patients with intervals greater than 35 days are omitted.

fever and did not represent a new respiratory illness. The second patient exhibited exudative pharyngitis and the initial antistreptolysin titer was 125 which later increased to 250 units. He gave no history of a prior respiratory illness. Thus, in this patient the rheumatic symptoms appeared without a latent period.

The relationship of the length of the latent period to the type of infecting organism is presented in Table 4. There were 10 different types causing the initial infection in addition to the 5 patients from whom a non-typable strain was isolated. The majority of infections was due to type 14. The relative frequency of the types isolated paralleled the frequency with which these types were present in other patients with streptococcal pharyngitis who did not develop rheumatic fever. The length of the latent period did not appear to be a function of any particular type.

The relationship of the latent period to the titer of antistreptolysin in the acute phase sera as well as to the average increase in titer demon-

strated during convalescence is shown in Table 5. No definite conclusion can be made regarding the average initial titers or the average increase in titers in those patients with short or long latent periods. It is possible that the slightly higher average initial titers exhibited by the 5 patients in the 0-5 day interval is due to the fact that these patients had already experienced an increase in antibody at the time the initial, acute phase sera were obtained. This suggestion is confirmed by the relatively small in-

TABLE 5. THE RELATIONSHIP OF THE LATENT PERIOD TO ANTISTREPTOLYSIN TITERS

<i>Latent period (days)</i>	<i>Number of patients*</i>	<i>Average antistreptolysin titer</i>	
		<i>Initial</i>	<i>Increase at 3 weeks</i>
0-2	2	313	125
3-5	3	187	51
6-8	5	99	336
9-11	8	137	492
12-14	16	173	332
15-17	11	100	256
18-20	18	109	409
21-23	14	136	240
24-26	16	119	208
27-29	5	142	228
30-32	5	175	233
33-35	4	96	263
Greater than 35	11	150	471

\* Includes only those patients with acute and convalescent sera who had experienced a single infection and who received no specific therapy.

crease in antistreptolysin demonstrated in the convalescent sera. Thus, some of these 5 patients must have acquired a streptococcal infection at least one week prior to the observed illness. Since the numbers of patients in each time interval were small, the 107 patients with intervals of 35 days or less were divided into two groups, one with initial antistreptolysin titers of 200 units or greater and the other with titers of less than 200 units. The average latent period for the group with initial titers above 200 units was 16 days. The average period of the group with initial titer below 200 was 19 days, a difference which is not significant.

The 38 patients who carried two different serologic types of group A streptococci did exhibit a different pattern of latent periods than the 127 patients who showed only one type in the two cultures. There were no

patients with a latent period of less than 8 days. However, for technical reasons it might have been difficult to establish the presence of two infections within a week of the observed respiratory illness. There was an increased number of patients with long latent periods; 21 cases or 55 per cent of the total group developed rheumatic fever more than 35 days after the onset of the observed illness. Of this group of 21 cases with a prolonged latent period, 7 had received an antibiotic as therapy for the observed streptococcal infection, whereas only 2 of the remaining 17 cases were given specific treatment. The second, streptococcal infection, usually inapparent clinically, was probably related directly to the rheumatic attack and accounted for the prolonged latent period in many of these patients.

The distribution of the latent periods of individuals who received antibiotics but showed no bacteriological evidence of an intervening new streptococcal infection is considerably different than the intervals exhibited by those 127 patients who received no therapy. Of the former, 26 per cent, as compared to 9 per cent of the latter group, exhibited latent periods of 8 days or less. The antistreptolysin titers of the acute phase sera from the 5 patients developing rheumatic fever at about the same time as the streptococcal respiratory illness began were 83, 83, 250, 317, and 625 indicating that in all probability 2 or 3 patients had recently experienced a streptococcal infection. Since some patients early in the course of acute rheumatic fever experience a recurrence of the symptom, soreness of the throat, it is possible that some of these short latent periods are an artifact. In addition, it should be recalled that approximately half of all patients with respiratory infections received antibiotics, so that if therapy did not alter the incidence of rheumatic fever in those patients who were destined to develop this complication after a very short latent period, the actual number observed in this category should approximate the number observed in the group of 127 patients who experienced a single infection and received no therapy. The figures show that there were 11 cases in both groups whose latent period was less than 8 days. Thus, it appears probable that treatment of the streptococcal infection is not likely to decrease the attack rate of rheumatic fever in patients with short latent periods.

The distribution of the latent periods in those patients whose initial culture failed to show group A streptococci is difficult to explain. Of the 6 patients developing rheumatic fever during the first time interval, streptococci were isolated from 4 a few days later. The initial antistreptolysin titer was available from 5 of the 6 patients. In 3 it was 83, and the re-



maining initial titers were 100 and 250. Of the total group 18 showed a positive culture during the latent period. Some of these acquisitions probably represent a new infection, accounting for the relatively large number of patients with long latent periods.

#### DISCUSSION

Our concept of the latent period in acute rheumatic fever has been derived from historical information obtained from the patient at the time the rheumatic symptoms appeared rather than from observations of patients with streptococcal infections who subsequently developed signs of rheumatic activity. Data obtained by the former method tend to be inaccurate since the memory of the patient concerning events occurring several weeks earlier is frequently poor, and the etiology of the preceding respiratory illness cannot be defined. In addition, the studies of Rantz, Boisvert and Spink<sup>4</sup> indicate that reinfection with a second type of group A streptococcus may occur during the latent period without associated overt clinical symptoms. Further errors are likely to occur because at least 14 per cent of patients with acute rheumatic fever give no history of a preceding illness and in another 24 per cent the streptococcal illness is so mild that the details are soon forgotten.<sup>10</sup>

In the population of 565 patients with acute rheumatic fever 48 per cent had been observed previously with an acute respiratory illness of sufficient severity to require hospitalization. In all but 23 an accurate history of the time of onsets of the streptococcal infection and rheumatic fever were obtained. Since routine cultures were obtained at the beginning of the respiratory illness, again three weeks later, and at the time of appearance of acute rheumatic fever, reinfections with new types of streptococci could be documented. Thus, it was possible to gain an accurate description of the latent period in a large group of patients. Such data provide information of both theoretical and practical value.

The normal distribution curve of the duration of the latent periods was based on 127 patients who received no therapy. The majority was thought to have experienced a single preceding streptococcal infection as determined by routine bacteriological studies. It was recognized that a few patients exhibiting a very short latent period may have actually acquired a clinically inapparent infection some weeks prior to the observed respiratory illness, and the observed illness actually represented the recurrence of sore throat which some patients with acute rheumatic fever experience. In favor of this interpretation is the high titer of antistreptolysin in the acute phase serum of some patients showing a short latent period. In

addition, it appeared reasonable to assume that the majority of patients who exhibited a latent period of over 35 days probably had experienced a second, clinically inapparent streptococcal infection which was not detected by the techniques employed.

The length of the latent period did not appear to be related to the type of streptococcus responsible for the respiratory illness nor did it appear to vary with the magnitude of the antibody response to infection as measured by antistreptolysin. There was a slight difference in the average latent periods of those patients with an initial antistreptolysin titer of less than 200 units and those with greater than 200 units. The average periods were 19 and 16 days, respectively. This difference may have been produced by a few patients who had experienced an inapparent streptococcal infection a few days or weeks prior to the observed illness. Thus, the initial antistreptolysin titer would be high and the latent period short in such patients. Since the difference in the latent periods between the two groups was not great, it may be concluded that few such cases were included in this analysis.

Of the 127 patients, 21 were experiencing a recurrent attack of acute rheumatic fever, and in these there was no indication that the latent period was shortened. It has been reported that recurrent attacks are not associated with shorter latent periods<sup>11</sup> but no published data are available to support such a statement. More extensive information on this subject would be valuable since rheumatic fever has been compared to serum sickness in which the readministration of the responsible antigen results in an accelerated reaction.

As indicated earlier, Rantz, Boisvert and Spink<sup>4</sup> suggested that reinfection with a new serological type during the latent period might be causally related to the development of acute rheumatic fever. The present analysis does not permit a comparison of attack rates in patients with one and two infections. However, some information is available from a study of reinfections in 5198 patients with streptococcal infections observed at the same military installation between January 1949 and January 1954<sup>8</sup> All of these patients received antibiotics and only a *single* convalescent culture was obtained from each. The incidence of reinfection was 10 per cent, whereas in the present study 15 per cent of the patients with rheumatic fever showed two organisms during the latent period. Reinfections were especially prevalent among those patients with long latent periods. Indeed, if only those patients with latent periods of less than 36 days are considered, 9 per cent experienced a second infection, a figure which is similar to the 10 per cent figure observed in the population quoted above.

Thus, the present data do not support the view that two closely spaced infections play a major role in the causation of rheumatic fever.

The curve showing the distribution of cases of rheumatic fever according to the length of the latent period should be of practical value to the pediatrician, internist, and family physician. It is a well established fact that proper therapy of the streptococcal infection with penicillin will prevent acute rheumatic fever and, presumably rheumatic carditis. Treatment initiated at the onset of symptoms of the streptococcal infection might be expected to fail to eliminate those attacks of rheumatic fever that develop

TABLE 6. MAXIMAL POSSIBLE EFFECT OF THERAPY OF STREPTOCOCCAL INFECTIONS ON THE OCCURRENCE OF RHEUMATIC FEVER ACCORDING TO THE TIME OF INSTITUTION OF TREATMENT

<i>Time therapy instituted*</i> (days)	<i>Per cent reduction of acute rheumatic fever†</i>
0	98
8	90
14	67
21	42
29	8

\* Expressed in days from onset of first symptom of the respiratory illness.

† Calculations are based on the assumption that adequate therapy will prevent all rheumatic fever except those cases occurring through the second day. Rheumatic fever developing after 35 days is considered not to be affected by therapy.

in the first two days. This represents approximately 2 per cent of all rheumatic attacks. The present data as well as those obtained during the course of another study<sup>9</sup> support this conclusion. More important, however, is the fact that therapy with penicillin will prevent rheumatic fever even when it is administered after the patient has fully recovered from the immediate effects of the streptococcal infection. In the only study reported,<sup>10</sup> penicillin therapy was initiated nine days after the onset of the acute respiratory illness at a time when the patients were asymptomatic. The reduction in the attack rate of rheumatic fever in those developing symptoms between 10 and 35 days was 82 per cent as compared to a control group of patients.

If the assumption is made that *adequate* therapy of the streptococcal infection instituted at any time during the latent period will prevent all subsequent attacks of rheumatic fever except those developing within the first 2 days and those appearing after an interval of 35 days, then therapy initiated at the times indicated in Table 6 will reduce the total number of

cases of rheumatic fever by the amounts indicated. These data would indicate that the physician who makes a diagnosis of a streptococcal infection in one patient should then determine the dates of onset of sore throat in other household contacts. Those contacts whose respiratory symptoms developed during the preceding month and who received no specific therapy during the acute illness should be placed on treatment with penicillin for the prevention of rheumatic fever. Ideally, oropharyngeal cultures from all contacts should also be obtained, since some infections will produce no symptoms and such individuals should receive the benefit of specific therapy.

#### SUMMARY

The latent period between the onset of the streptococcal infection and the onset of acute rheumatic fever was determined in 251 patients. In 113 of these patients an infection by a single type of streptococcus occurred and the patient received no specific therapy. In this group the mean latent period was 18.6 days. There was no correlation between the type of group A streptococcus causing the infection and the length of the latent period. Patients who had experienced a prior attack of rheumatic fever did not exhibit an accelerated onset of rheumatic symptoms. The length of the latent period did not appear to be related to the magnitude of the antistreptolysin response to infection.

Reinfection with a new type of streptococcus during the latent period did not prove to be important in the causation of rheumatic fever, but it was associated with prolongation of the latent period in many instances.

On the basis of this analysis it is recommended that patients with streptococcal infections should receive therapy with penicillin for the prevention of rheumatic fever even though the onset of respiratory symptoms was as long as four weeks previously.

#### REFERENCES

1. Paul, J. R.: *The epidemiology of rheumatic fever*. 3d ed., New York, American Heart Association, 1957, pp. 33-36.
2. Dixon, F. J., Feldman, J. D., and Vazquez, J. J.: Experimental glomerulonephritis. The pathogenesis of a laboratory model resembling the spectrum of human glomerulonephritis. *J. exp. Med.*, 1961, *113*, 899-920.
3. Schlesinger, B.: The relationship of throat infection to acute rheumatism in childhood. *Arch. Dis. Child.*, 1930, *5*, 411-430.
4. Rantz, L. A., Boisvert, P. J., and Spink, W. W.: Etiology and pathogenesis of rheumatic fever. *Arch. intern. Med.*, 1945, *76*, 131-138.
5. Jones, T. D.: Diagnosis of rheumatic fever. *J. Amer. med. Ass.*, 1944, *126*, 481.
6. Wannamaker, L. W., Rammelkamp, C. H., Jr., Denny, F. W., Brink, W. R., Houser, H. B., Hahn, E. O., and Dingle, J. H.: Prophylaxis of acute rheu-

- matic fever by treatment of the preceding streptococcal infection with various amounts of depot penicillin. *Amer. J. Med.*, 1951, 10, 673-695.
7. Swift, H. F., Wilson, A. T., and Lancefield, R. C.: Typing group A streptococci by M precipitin reactions in capillary pipettes. *J. exp. Med.*, 1943, 78, 127.
  8. Houser, H. B., Eckhardt, G. C., Hahn, E. O., Denny, F. W., Wannamaker, L. W., and Rammelkamp, C. H., Jr.: Effect of aureomycin treatment of streptococcal sore throat on the streptococcal carrier state, the immunologic response of the host, and the incidence of acute rheumatic fever. *Pediatrics*, 1953, 12, 593-606.
  9. Catanzaro, F. J., Rammelkamp, C. H., Jr., and Chamovitz, R.: Prevention of rheumatic fever by treatment of streptococcal infections. II. Factors responsible for failures. *New Engl. J. Med.*, 1958, 259, 51-57.
  10. Rammelkamp, C. H., Jr., Houser, H. B., Hahn, E. O., Wannamaker, L. W., Denny, F. W., and Eckhardt, G. C.: *The prevention of rheumatic fever*. Pp. 304-315 in *Rheumatic fever, a symposium*. L. Thomas, Ed., Minneapolis, University of Minnesota Press, 1952.
  11. Seegal, D. and Earle, D. P., Jr.: A consideration of certain biological differences between glomerulonephritis and rheumatic fever. *Amer. J. med. Sci.*, 1941, 201, 528-539.
  12. Catanzaro, F. J., Stetson, C. A., Morris, A. J., Chamovitz, R., Rammelkamp, C. H., Jr., Stolzer, B. L., and Perry, W. D.: The role of the streptococcus in the pathogenesis of rheumatic fever. *Amer. J. Med.*, 1954, 17, 749-756.