

## THE SERUM ANTISTREPTOLYSIN TITER IN CHRONIC GLOMERULONEPHRITIS

David P. Earle Jr., ... , John D. Lyttle, Elizabeth L. Jost

*J Clin Invest.* 1942;21(4):483-489. <https://doi.org/10.1172/JCI101324>.

Research Article

Find the latest version:

<https://jci.me/101324/pdf>



## THE SERUM ANTISTREPTOLYSIN TITER IN CHRONIC GLOMERULONEPHRITIS

By DAVID P. EARLE, JR., EMILY N. LOEB, DAVID SEEGAL, JOHN D. LYTTLE,  
AND ELIZABETH L. JOST

(From the Research Service, First Division, Welfare Hospital, Department of Hospitals;  
Presbyterian Hospital; Babies Hospital; and the Departments of Medicine and Pediatrics,  
College of Physicians and Surgeons, Columbia University, New York City)

(Received for publication March 6, 1942)

Previous reports (1, 2, 3) have dealt with the serum antistreptolysin titer response in acute glomerulonephritis. Seegal, Lyttle and their associates (2) found that 94 per cent of 116 consecutive cases of acute glomerulonephritis were associated with significant rises in antistreptolysin titer. Longcope (3) found an increased antistreptolysin titer in the acute stage of 72 per cent of 36 cases of acute hemorrhagic nephritis (type A). These studies show that the *acute* infections, which so typically precede the onset of acute glomerulonephritis, are generally due to the group A hemolytic streptococcus. Winkenwerder, McLeod and Baker (4), however, described another type of glomerulonephritis (type B), characterized by an insidious onset of edema and a progressive downhill course, and usually associated with *chronic* upper respiratory infection. Although group A hemolytic streptococci were often recovered from the upper respiratory passages of these patients (type B), Longcope (3) showed that rises in antistreptolysin titer were a rarity. Indeed, the titers were frequently found to be abnormally low.

The present study is based on the examination of the serum antistreptolysin titer response in patients with chronic glomerulonephritis. The case material consists of 81 patients who have been studied at the Nephritis-Hypertension Clinic of Dr. Dana W. Atchley and Dr. Robert F. Loeb at the Presbyterian Hospital, a similar clinic of Dr. John D. Lyttle at the Babies Hospital, and at the Research Service of the First Division of the Welfare Hospital.

This study was undertaken with full knowledge of the difficulty of establishing the diagnosis of chronic glomerulonephritis. In this series of 81 patients presenting the picture of chronic glomerulonephritis, 24 are known to have died. Autopsies performed on 13 of these revealed chronic glo-

merulonephritis. A biopsy of the kidney established the diagnosis in one additional case. In 23 other cases, attacks typical either of acute glomerulonephritis, *i.e.*, the onset of the disease, or of an exacerbation of chronic glomerulonephritis, have been observed. Thus, the diagnosis of glomerulonephritis seems to have been established beyond doubt in 37 of the 81 cases. The remaining 44 patients were thoroughly studied and, in the opinion of several experienced observers, there was no evidence of renal disease other than chronic glomerulonephritis.

The patients comprising this study have been observed over periods of from 4 months to 8 years. Twelve patients were followed for less than one year, the short follow-up being due to early death in 10 instances. Fifty-two, or 64 per cent, were followed for 2 or more years. Sera for the determination of the antistreptolysin titer were obtained at varying intervals in each patient. In hospitalized cases, determinations were made once or twice a week. It was not possible to obtain tests with this frequency in the ambulatory patients seen at the clinic. However, in the majority of these instances, determinations were made at intervals of from 1 to 4 months. In addition, the patients were instructed to report to the clinic whenever an infection developed and were then studied weekly.

Todd (5) developed the technique for the determination of serum antistreptolysin and with minor modifications (2) this technique has been employed throughout the present studies. The antistreptolysin value is determined by the minimum amount of serum necessary to neutralize a standard amount of streptolysin. The value may be recorded either as the amount of serum in fractions of cubic centimeters necessary for the neutralization of the streptolysin, or as units which are calculated as the reciprocal of the frac-

tion of cubic centimeters. The latter method was used throughout this study. An increase in serum antistreptolysin value may be represented as the maximum value attained in the rise or as the rise in titer over base-line determinations in individual patients.

A significant increase in serum antistreptolysin has been shown to indicate group A hemolytic streptococcal infection, since a variety of infections and other diseases are not followed by increases in the titer of this antibody (3, 5, 6). Mote and Jones (6), in a study of the antistreptolysin titer response of 811 "healthy" subjects and 525 "sick" individuals, state that, ". . . in no instance was the titer observed to increase in an individual in whom infection by the hemolytic streptococcus could be definitely excluded."

#### CRITERIA FOR RISE IN ANTISTREPTOLYSIN TITER

In order that a rise in serum antistreptolysin titer be considered significant, it was required that:

1. The increase in the titer reading be represented by at least 2 decrements of 0.1 ml. of standard diluted serum over well-established base-line determinations for the individual patient. With the exception of 1 instance, each rise in the present study accepted as significant was based on 3 or more such decrements.

2. The individual titer values of the rise oc-

cur in a progressively increasing or decreasing (or both) curve. Thus, erratic fluctuations in titer (as shown in Figure 1) were not accepted as significant.

In order to determine the true maximum value of a rise in antistreptolysin titer, it was further required that at least one test be available within 3 weeks of the onset of an infection; or, in a few instances, that the antistreptolysin titer curve be still rising toward a maximum, if the first titer of the rise was determined on serum withdrawn more than 3 weeks after the onset of an infection.

#### SUMMARY OF MATERIAL

There were 101 significant antistreptolysin titer rises occurring in 61 cases. Eighty-five of these rises form the basis of this study.<sup>1</sup>

<sup>1</sup> In addition to the 16 rises in titer whose maxima were not apparent, 36 other instances of variations in antistreptolysin titer were discarded for the following reasons: (a) In two instances, clear cut end points in the antistreptolysin titrations could not be obtained. In both cases, the sera were very lipemic. In one, the rise was associated with a group A hemolytic streptococcus tonsillitis, while no infection was present in the other. (b) In 17 instances, the variations in antistreptolysin titer fluctuated without a definite trend being apparent. Several such fluctuations may be seen in Figure 1. Eight of these occurred in patients with edema. In 11 instances, there was no evidence of infection, while the remaining 6 gave histories of frequent head colds. In no instances

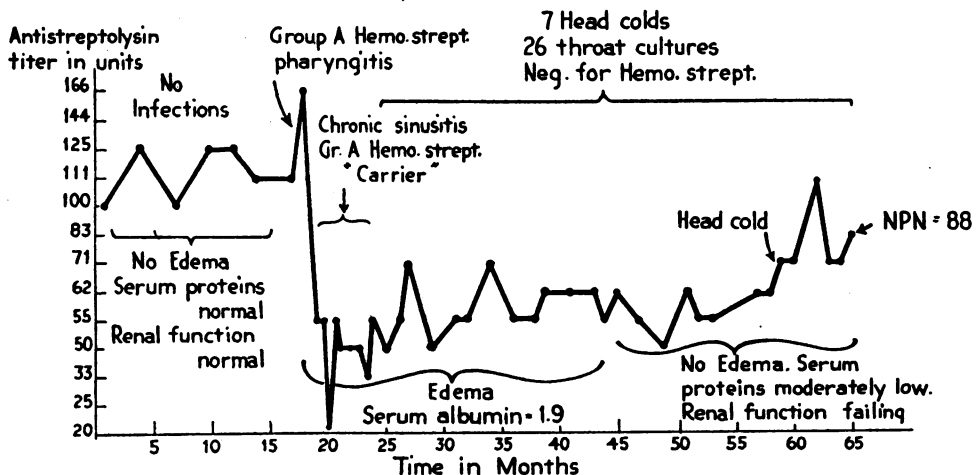


FIG. 1. ANTISTREPTOLYSIN TITER CURVE OF PATIENT WITH CHRONIC GLOMERULONEPHRITIS SHOWING LOW TITERS ASSOCIATED WITH ONSET OF NEPHROTIC STAGE, ALTHOUGH GROUP A HEMOLYTIC STREPTOCOCCI WERE PRESENT IN THROAT CULTURES DURING FIRST 6 MONTHS OF NEPHROTIC STAGE

It should be noted that there were no variations of antistreptolysin titer in 8 of the 81 patients with chronic glomerulonephritis. These 8 patients were followed over periods of from 8 to 102 months, with an average of 35 months per patient. An average of 21 antistreptolysin determinations per patient was made, with a range of 7 to 84. An analysis of these cases indicated no striking differences in their clinical course as compared with that of the cases showing rises in titer.

The data presented in the foregoing sections are summarized in Table I.

TABLE I

*Summary of antistreptolysin titer data in 81 cases of chronic glomerulonephritis*

- 101 definite rises in 61 cases.
- 85 rises in 56 cases, with sufficient data to indicate the maximum titer of the rise.
- 16 rises with insufficient data to indicate the maximum titer of the rise.
- 36 questionable rises in 28 cases (includes some of the cases above).
- 8 cases with no variation of antistreptolysin titer in period of study (8 to 102 months).

RELATION OF SEX AND AGE TO ANTISTREPTOLYSIN TITER RESPONSE

Sex did not appear to modify the antistreptolysin titer response. Of the 81 cases analyzed, 49 were males and 32 females. Forty-eight of the adequately studied rises in antistreptolysin titer occurred in male patients, 37 in female patients. Table II summarizes the sex incidence in relation to the maximum values of the antistreptolysin titer rises.

With respect to age, the rises in antistreptolysin titer were, in general, greater among the children than among the adults. These data are sum-

TABLE II

*Sex distribution of small, medium and large rises in antistreptolysin titer in chronic glomerulonephritis*

Maximum titer of rise	Number in 35 male patients	Number in 21 female patients
125 units or less (small).....	24	16
144 units to 250 (medium).....	14	15
333 units or more (large).....	10	6

were the throat cultures positive for hemolytic streptococci. (c) In 17 instances, the rise in titer was indicated by a single determination. In 12 of these, there were gaps of 2 or more months between the titer showing the rise and the nearest base-line determinations.

TABLE III

*Age distribution of small, medium and large rises in antistreptolysin titer in chronic glomerulonephritis*

Maximum titer of rise	Number of rises in 5 patients, 1 to 9 years of age	Number of rises in 28 patients, 10 to 19 years of age	Number of rises in 48 patients, 20 or more years of age
125 units or less.....	0	17	23
144 units to 250.....	7	7	15
333 units or more.....	4	9	3
Total rises.....	11	33	41

marized in Table III. It is possible that the severity of the hemolytic streptococcal infections may have played a role in this difference, but the number of children in this series was not large enough to determine this point.

RELATION OF INFECTION TO ANTISTREPTOLYSIN TITER RESPONSE

A culture was taken of each patient's throat at every visit to the clinic. Routine throat cultures were taken of hospitalized patients twice a week. Cultures were taken daily or every other day in hospitalized patients if there was any suspicion of infection. In addition, the patient was questioned in regard to the symptoms indicative of infection, and examinations of the nose, pharynx and cervical lymph nodes were made at each clinic visit, and at appropriate intervals in hospitalized cases. The throat cultures were classified as positive or negative for group A hemolytic streptococci. Infections, if present, were classified as chronic or acute. The acute infections were further subdivided into "deep" or "superficial" groups, following the scheme previously reported (1). Deep infections included mastoiditis, peritonsillar or cervical abscess, moderate or severe cervical lymphadenitis, otitis media and sinusitis. Superficial infections included pharyngitis (usually with mild cervical adenitis) and the "common cold."

Fifteen of the 85 adequately studied rises in antistreptolysin titer were associated with deep, 67 with superficial, and 3 with no observed infections. Twenty per cent of the rises in titer following deep infections attained a maximum of 333 units or more (large rises), 33 per cent reached from 144 to 250 units (medium rises), and 47 per cent reached a maximum of 125 units or less (small rises). The superficial infections

showed an almost identical distribution, namely 19, 33 and 48 per cent, followed respectively by large, medium and small rises in antistreptolysin titer. In summary, the magnitude of the antistreptolysin titer response among these patients with chronic glomerulonephritis was unrelated to the deep or superficial character of hemolytic streptococcal infection.

The percentage of rises in antistreptolysin titer associated with the presence of group A hemolytic streptococci and the presence or absence of infection are summarized in Table IV. Since a rise

TABLE IV

*Percentage of small, medium and large antistreptolysin titer rises associated with cultures showing Group A hemolytic streptococci and with infections in patients with chronic glomerulonephritis*

Maximum titer of rise	Number of rises	Rises with Group A hemolytic streptococci in cultures	Rises with infection		
			Acute	Chronic	None observed
		<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
125 units or less . . .	40	42	78	20	2
144 units to 250 . . .	29	52	79	14	7
333 units or more . . .	16	75	100	0	0
All rises . . . . .	85	52			

in antistreptolysin titer is confined to infections caused by hemolytic streptococci, usually Group A, it is apparent that this test was of definite value in determining the etiology of many infections occurring in patients with chronic glomerulonephritis.

These data indicate that rises in antistreptolysin titer that attain a maximum of 333 units or more are associated with a higher incidence of cultures showing group A hemolytic streptococci than are the smaller rises. Likewise, the greater rises are all associated with acute infection, while 22 per cent of the small rises and 21 per cent of the medium rises are associated either with chronic infection or with no observed infection.

#### GROUP A HEMOLYTIC STREPTOCOCCAL INFECTION WITHOUT RISE IN ANTISTREPTOLYSIN TITER

In this series of 81 patients with chronic glomerulonephritis, there were 5 acute infections (1, otitis media; 1, bronchitis; and 3, pharyngitis) apparently due to group A hemolytic streptococci,

wherein adequate antistreptolysin titer studies revealed no subsequent rise in titer. Three of these occurred in patients with edema, 2 in patients without edema. All but one of these infections occurred in patients who exhibited rises in titer at other times. Two of these infections occurred at a time when the titer was declining from a previous rise.

Several other acute group A hemolytic streptococcal infections were observed in which adequate antistreptolysin titer data were not obtained. On this account, these infections could not be included in the analysis of the antibody response.

#### GROUP A HEMOLYTIC STREPTOCOCCUS "CARRIER STATE"

There were 26 instances of the "carrier state" occurring in 20 patients. The "carrier state" in this study refers, arbitrarily, to instances in which group A hemolytic streptococci were recovered from the throats of individuals without evidence of acute upper respiratory infection and without significant rise in antistreptolysin titer. Occasionally only 1 or 2 isolated throat cultures were positive for hemolytic streptococci, but usually repeated cultures over periods of several weeks to as long as 6 months were positive. These "carrier states" were frequently but not invariably associated with chronic sinusitis and post-nasal discharge. It is recognized that these "carrier states" may represent actual hemolytic streptococcal infection. However, this seems unlikely in the majority of instances inasmuch as 18 of these 20 patients had responded to hemolytic streptococcal infections at other times with definite rises in antistreptolysin titer.

#### EFFECT OF NEPHROTIC PHASE ON ANTISTREPTOLYSIN TITER RESPONSE

Edema associated with low serum albumin and high serum cholesterol concentrations was considered to indicate the nephrotic phase of chronic glomerulonephritis. There were marked variations in the degree of edema and in the levels of serum albumin and cholesterol among the different cases, as well as in particular individuals. The problem was further confused by the occurrence, in some cases, of edema due to circulatory failure. In a few instances there was a possibility that

the edema and hypoproteinemia were due to malnutrition. However, the status of each patient at the time of a significant rise in antistreptolysin titer was evaluated and classified, to the best of our ability, as being either non-nephrotic or nephrotic. When this was done, it became apparent that the antistreptolysin titer responses to hemolytic streptococcal infections were significantly greater among the patients without edema than among those with edema. This is illustrated by Figure 2.

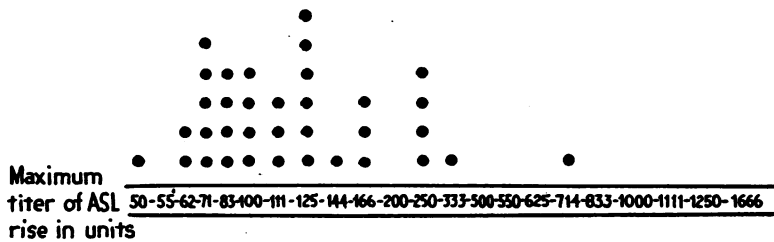
In addition, it should be noted that 18 of 26 group A hemolytic streptococcal carrier states oc-

curred in patients with the nephrotic element. Three of the 5 proven group A hemolytic streptococcal infections, not followed by a rise in titer, were also in the nephrotic group.

Although, as was previously indicated, there was a higher incidence of the greater rises in antistreptolysin titer among the younger patients than among the older groups, the height of the rise depended on the presence or absence of edema, as well as on the age distribution. This is illustrated in Table V.

Many patients with chronic glomerulonephritis have been observed during periods of transition

35 Rises in Patients with the Nephrotic Stage



50 Rises in Patients without the Nephrotic Stage

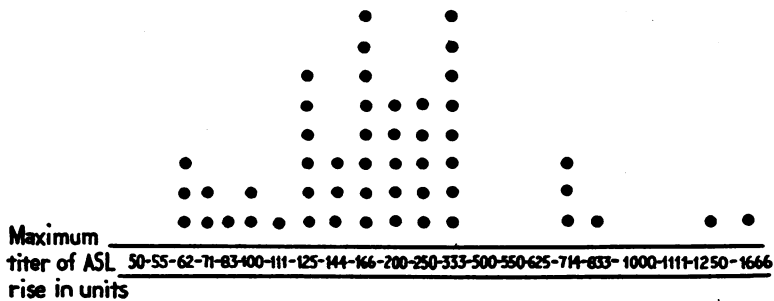


FIG. 2. DISTRIBUTION OF MAXIMA OF ANTISTREPTOLYSIN TITER RISES IN PATIENTS WITH CHRONIC GLOMERULONEPHRITIS, WITH AND WITHOUT EDEMA

TABLE V

Age distribution of small, medium and large rises in antistreptolysin titer occurring among patients with chronic glomerulonephritis and edema

Maximum titer of rise	Patients 9 years of age and under		Patients 10 to 19 years of age		Patients 20 and more years of age	
	Number of rises in cases with edema	Number of rises in cases without edema	Number of rises in cases with edema	Number of rises in cases without edema	Number of rises in cases with edema	Number of rises in cases without edema
125 units or less.....	0	0	12	5	13	10
144 units to 250.....	2	5	1	6	5	10
333 units or more.....	1	3	1	8	0	3

from the dry to the edematous phase of the disease, or *vice versa*. In 9 of these instances studied, significant changes in the base line level of the antistreptolysin titer were noted, the titer being higher in the non-edematous than in the edematous phase. Figure 1 is an illustration of this point. However, in other instances, similar changes in base line titers were not associated with changes from the nephrotic to non-nephrotic phase of chronic glomerulonephritis, or *vice versa*.

#### DISCUSSION

A rise in serum antistreptolysin titer was found to be of definite value in detecting group A hemolytic streptococcal infections, in the presence of negative throat cultures, among patients with chronic glomerulonephritis, as well as being of confirmatory value when the cultures were positive. This test was not infallible, since there were 5 acute infections associated with positive cultures for group A hemolytic streptococci which were not associated with rises in titer.

Males outnumbered females in this series. Sex did not significantly modify the antistreptolysin titer response. No previous study on antistreptolysin titer in various diseases has noted any positive effect of sex on the test.

With respect to age, the younger patients had, in general, greater rises in antistreptolysin titer following infection than did the older patients. Lyttle and his colleagues (2) reported a similar correlation in their study of the serum antistreptolysin titer in acute glomerulonephritis. Lippard and Johnson (7), however, found that rises in antistreptolysin titer following hemolytic streptococcal infections among children more than 17 months of age were comparable to those observed in adults. Infants under 17 months of age, in contrast, showed little tendency to exhibit rises in antistreptolysin titer. In cases of chorea, Bunim and McEwen (8) found "no strict correlation between the age of the patient, the severity of the chorea, and the height of the antistreptolysin titer." Mote and Jones (6) found that the incidence of rises in antistreptolysin titer was greater in younger "healthy" control subjects than in the older age groups, presumably because of "a higher incidence of very mild or subclinical respiratory infections in children." In their rheumatic

patients, age had no effect on the incidence of antistreptolysin titer response. They also stated that age had no effect on the magnitude of the response in these patients.

In the present series of 81 patients with chronic glomerulonephritis, it was found that the greater the magnitude of the rise in antistreptolysin titer, the greater was the frequency of positive cultures for group A hemolytic streptococci. It was also noted that the incidence of preceding acute infection was higher in the group showing larger rises in titer, than among those exhibiting the medium and small rises. However, whether the type of infection was "deep" or "superficial" apparently made no difference in the titer response.

Data have been presented (Figure 2) that indicate a smaller though definite response in antistreptolysin titer among patients with the nephrotic stage of chronic glomerulonephritis than among patients without edema. Previously Longcope (3) had noted that among his 19 cases of "type B" glomerulonephritis, characterized by nephrotic edema, the antistreptolysin titer was rarely above normal and was sometimes persistently very low. A severe hemolytic streptococcal tonsillitis in one of Longcope's nephrotic patients was followed by a rise in antistreptolysin titer that reached a maximum of only 100 units. As Longcope pointed out, the explanation for the low titers and small antistreptolysin response to hemolytic streptococcal infection in these patients is not clear.

In this connection, a recent study (9) has shown that the antistreptolysin titer of children with nephrosis is extremely low, usually less than 10 units, and that when the patient recovers the titer rises to the generally accepted normal range. Furthermore, when these individuals contract group A hemolytic streptococcal infections during the active phase of the nephrosis, in spite of very low base line titers, large rises in antistreptolysin titer ensue in many instances.

#### SUMMARY AND CONCLUSIONS

1. The serum antistreptolysin titer response was analysed in 81 cases of chronic glomerulonephritis, studied over periods of from 4 months to 8 years.

2. Rises in serum antistreptolysin titer occurring in patients with chronic glomerulonephritis

were of value in detecting the hemolytic streptococcal etiology of many infections in which group A hemolytic streptococci could not be isolated from the pharynx.

3. A number of instances of chronic upper respiratory infection were observed in which repeated cultures showed the presence of group A hemolytic streptococci. These instances unassociated with rises in antistreptolysin titer were designated as the "carrier state."

4. Certain factors affecting the antistreptolysin titer response in chronic glomerulonephritis were examined with the following results:

- a. Sex had no effect.
- b. In general, children exhibited greater titer response to infection than did adults.
- c. The character of the preceding hemolytic streptococcal infection ("deep" or "superficial") did not appear to affect the magnitude of the antistreptolysin titer response.
- d. In general, patients with "nephrotic" edema exhibited smaller rises in titer than did those without edema.

5. The relation of the serum antistreptolysin titer response to the exacerbation in chronic glomerulonephritis is discussed in the accompanying paper (10).

The authors are indebted to Miss Grace Davis and Mr. Walter Meyer for their technical assistance.

#### BIBLIOGRAPHY

1. Seegal, D., and Lyttle, J. D., Antistreptolysin titer of the serum in acute glomerulonephritis. *Proc. Soc. Exper. Biol. and Med.*, 1933, 31, 211.
2. Lyttle, J. D., Seegal, D., Loeb, E. N., and Jost, E. L.,

The serum antistreptolysin titer in acute glomerulonephritis. *J. Clin. Invest.*, 1938, 17, 631.

3. Longcope, W. T., Studies of the variations in the antistreptolysin titer of blood serum from patients with hemorrhagic nephritis. II. Observations on patients suffering from streptococcal infections, rheumatic fever, and acute and chronic hemorrhagic nephritis. *J. Clin. Invest.*, 1936, 15, 277.
4. Winkenwerder, W. L., McLeod, N., and Baker, M., Infection and hemorrhagic nephritis. *Arch. Int. Med.*, 1935, 56, 297.
5. Todd, E. W., Antihaemolysin titres in haemolytic streptococcal infections and their significance in rheumatic fever. *Brit. J. Exper. Path.*, 1932, 13, 248.
6. Mote, J. R., and Jones, T. D., Studies of hemolytic streptococcal antibodies in control groups, rheumatic fever, and rheumatoid arthritis. I. The incidence of antistreptolysin "O," antifibrinolysin, and hemolytic streptococcal precipitating antibodies in the sera of urban control groups. II. The frequency of antistreptolysin "O," antifibrinolysin, and precipitating-antibody responses in scarlet fever, hemolytic streptococcal infections, and rheumatic fever. III. The magnitude of antistreptolysin "O," antifibrinolysin, and precipitating-antibody responses; the persistence of the antibodies, and variations in antistreptolysin "O" curves in scarlet fever, hemolytic streptococcal infections, and rheumatic fever. *J. Immunol.*, 1941, 41, 35.
7. Lippard, V. W., and Johnson, P., Beta hemolytic streptococcal infection in infancy and in childhood. I. Antifibrinolysin and antistreptolysin response. *Am. J. Dis. Child.*, 1935, 49, 1411.
8. Bunim, J. J., and McEwen, C., The antistreptolysin titer in rheumatic fever, arthritis and other diseases. *J. Clin. Invest.*, 1940, 19, 75.
9. Lyttle, J. D., Seegal, D., Loeb, E. N., and Jost, E. L., The antistreptolysin titer in nephrosis. Unpublished observations.
10. Earle, D. P., Jr., Seegal, D., Lyttle, J. D., Loeb, E. N., and Jost, E. L., The relation of the serum antistreptolysin titer to the exacerbation in chronic glomerulonephritis. *J. Clin. Invest.*, 1942, 21, 491.