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the COMMISSION ON ACUTE RESPIRATORY DISEASES

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Research Article

STUDIES OF STREPTOCOCCAL FIBRINOLYSIS. IV. CLINICAL APPLICATION OF A QUANTITATIVE ANTIFIBRINOLYSIN TEST [1]

BY THE COMMISSION ON ACUTE RESPIRATORY DISEASES [2]

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Although the antifibrinolysin test as originally described (1) is only qualitative in nature (2), it has proved valuable in the study of infections caused by the β-hemolytic streptococcus. However, the results obtained by different investigators have been difficult to interpret primarily because of failure to control the various factors participating in the fibrinolysin-antifibrinolysin reaction.

Recent studies (3) have clarified the nature of the reaction between fibrinolysin and antifibrinolysin. By control of the various participating factors, an antifibrinolysin test which is quantitative in nature has been devised (4) (5). The definition of the unit of measure (5) should result in more uniformity in reporting data concerning antifibrinolysin. Furthermore, the substitution of a clot formed from fibrinogen and thrombin for fresh plasma makes the test readily adaptable to the study of sera in a routine manner.

The present study was undertaken to evaluate the clinical usefulness of the quantitative antifibrinolysin test. The data have been analyzed from the standpoint of establishing: (*1*) the normal range of antifibrinolysin titers in healthy subjects; (*2*) the frequency with which β-hemolytic streptococcal infections stimulate an antifibrinolysin response; and (*3*) the specificity of the antifibrinolysin response.

MATERIALS AND METHODS

The data on antibody titers reported herein were obtained from tests made on sera collected from a group of 404 well soldiers and from 808 men admitted to the respiratory wards of the Regional Station Hospital No. 2, Fort Bragg, North Carolina. The blood was collected in sterile containers and the serum allowed to separate at room temperature. Prior to the determination of streptococcal antibodies the sera were stored at 4° C.

Throat cultures were obtained by swabbing both tonsils or tonsillar fossae and the posterior pharynx. In the majority of hospitalized patients the swabs were placed immediately in 4 ml. of broth, and after thorough mixing, a loopful was streaked on a meat infusion agar plate containing 5 per cent mule blood. Swabs from about half of the healthy soldiers studied were streaked directly on blood agar plates. Colonies of β-hemolytic streptococci were grouped and typed [3] by the capillary tube precipitin technique of Swift, Wilson and Lancefield (6). After serological identification of the organisms, the original strains were lyophilized and stored for future study.

The quantitative antifibrinolysin determinations [4] were made according to the technique described in detail elsewhere (5). The antistreptolysin "O" titers were determined by the method of Swift and Hodge (7). In both the antifibrinolysin and antistreptolysin titrations, a difference in titer of two successive tube dilutions between acute-phase and convalescent sera was considered significant.

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[3] Type specific rabbit sera were supplied through the generosity of Drs. Rebecca C. Lancefield and Homer F. Swift.

[4] Human fibrinogen was obtained through the courtesy of Drs. E. J. Cohn, S. Howard Armstrong, Jr. and John T. Edsall. The products of plasma fractionation employed in this work were developed from blood, collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, Mass., under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

RESULTS

Normal range of antifibrinolysin antibodies

Although an estimation of antifibrinolysin antibodies based on a single serum is not sufficient to establish an etiological relationship of the β-hemolytic streptococcus to the disease state, single determinations may be used as evidence of past experience with the organism if the level of antibody in normal subjects is well established. The normal group of subjects in this study was selected with a view toward determining those factors which might influence the titer of antifibrinolysin antibodies.

In the fall and winter 1943–44, a group of soldiers on active duty was interviewed, usually at weekly intervals, for a period of 3 to 8 weeks. During this time there were 404 men who failed to develop a respiratory illness of sufficient severity to require hospitalization, although a number had minor respiratory complaints. A blood specimen was obtained at the time of the first examination and from 392 subjects again 21 to 60 days later. From 3 to 8 cultures of the throat were taken at weekly intervals on each individual during the period of study.

To establish the normal range of antifibrinolysin antibodies, it was necessary that determinations be made on sera collected from subjects without clinical or bacteriological evidence of recent streptococcal infections. By the use of the titers obtained on the second specimen of serum collected on the above subjects it was possible to fulfill these criteria. Thus the normal group included only those men who were known to be free of clinical evidence of streptococcal infection and whose oropharynx failed to show β-hemolytic streptococci on culture. The distribution of titers in the healthy subjects who harbored either group A or other groups of β-hemolytic streptococci were included in a separate category in order to determine the effect of the carrier state on the level of antifibrinolysin antibodies.

As shown in Table I, approximately 87 per cent of the antifibrinolysin titers in the group of 236 men who never harbored β-hemolytic streptococci measured 150 units or less, and 43 per cent were less than 50 units. Because a large number of sera showed a titer of less than 50 units, 44 sera with such a titer were re-examined at lower dilution increments and it was found that in 28 samples the titer was 4 units or less. It would thus appear that the sera of approximately 27 per cent of normal subjects possess practically no antifibrinolytic property.

Healthy subjects who harbored β-hemolytic streptococci of group A or other groups prior to testing showed only a slightly different distribution of the antibody titer. For example, whereas 11 per cent of soldiers from whom no streptococci were isolated exhibited titers greater than 150 units, about 15 per cent of sera from subjects harboring β-hemolytic streptococci showed such titers. It seems likely that this slight difference was due to past infection in a few of the men who carried streptococci. There was no

TABLE I

Distribution of antifibrinolysin titers in well soldiers

Throat cultures*	Antifibrinolysin titers													Totals
	<50	50	100	150	200	300	400	500	600	800	1000	1400	1800	
No β-hemolytic strep.														
Number of sera	102	53	28	24	16	4	5	2		1	1			236
Per cent	43.2	22.4	11.8	10.1	6.7	1.6	2.0	0.8		0.4	0.4			
β-hemolytic strep. present														
Group A:														
Number of sera	32	16	9	14	4	2	1	2	2	1	1			84
Per cent	38.0	19.0	10.8	16.6	4.4	2.3	1.1	2.3	2.3	1.1	1.1			
Other than group A:														
Number of sera	25	18	4	14	3	2	5			1				72
Per cent	34.7	25.0	5.5	19.4	4.1	2.7	6.9			1.3				
Total sera	159	87	41	52	23	8	11	4	2	3	2			392

* Throat cultures were obtained during a period of 3 to 8 weeks prior to the blood specimen.

TABLE II

Correlation of antifibrinolysin titers with antistreptolysin titers in well soldiers

Antistreptolysin titer of initial sera	Antifibrinolysin titer of initial sera												
	<50	50	100	150	200	300	400	500	600	800	1000	1400	Totals
<50	7	1	1										9
50	7	4	3		1								15
62	19	3	3	3	1								29
83	14	5	3	2				1					25
100	20	10	5	5	2								42
125	27	11	6	14	3	2							63
159	19	12	6	8	5	2	3	1					56
200	20	10	5	3	1	1	2				1		43
250	12	10	9	8	4	1	1	2					47
317	9	7	5	5	1	1	1		1	2	1	1	34
400	4	6	1	5	4								20
500	1	1	3	2	1	2	1		1				12
625		3		1						1			5
833	1	1											2
1000		1				1							2
Totals	160	85	50	56	23	10	8	4	2	3	2	1	404

significant difference in the distribution of titers among the soldiers harboring group A as compared with other groups of β-hemolytic streptococci.

As shown in Table I, 11 per cent of sera in the subjects without evidence of recent streptococcal infection exhibited titers of antifibrinolysin greater than 150 units. The cause of the increased resistance in the sera of these subjects was not known, although the observation is in agreement with studies made on normal subjects using the method of Tillett and Garner for estimation of antifibrinolysin (8).

In order to obtain evidence concerning the specificity of elevated antifibrinolysin titers in normal subjects, a comparative study was made of the antistreptolysin and antifibrinolysin levels of the initial samples of sera collected from 404 healthy soldiers. These antibody titers are recorded in Table II. In general, the data showed that a high antifibrinolysin titer was associated with an elevated antistreptolysin titer. For example, there were 53 sera in which the antifibrinolysin titer was greater than 150 units, and in 43 of these the antistreptolysin titer was 159 or above. Since it is generally accepted that elevated antistreptolysin titers are indicative of past infection by the β-hemolytic streptococcus, the data presented in Table II suggest that elevated antifibrinolysin titers are due to previous streptococcal infection.

Previous investigations have shown (9) and the results of this study also demonstrated that a high antistreptolysin titer was not necessarily associated with an elevation of the titer of antifibrinolysin antibodies. There were 221 subjects whose sera were found to have an antistreptolysin concentration of 159 units or greater, and only 43 or 19 per cent had an antifibrinolysin titer above 150 units. This would indicate, therefore, that many streptococcal infections, as evidenced by elevated antistreptolysin titers, are not followed by an elevation of antifibrinolysin antibodies.

Antifibrinolysin response to infection

That the plasma clots of subjects with hemolytic streptococcal infections exhibit resistance to fibrinolysis during convalescence is well established. However, the observed frequency with which antifibrinolytic properties may be demonstrated in the blood following infection caused by the streptococcus has varied considerably. This variation in the response of the host may be due to difference in (*1*) the methods used to measure antifibrinolysin, (*2*) the time in convalescence serum specimens are obtained for testing, (*3*) the criteria used to establish the diagnosis of a streptococcal infection, (*4*) the antigenic properties of the infecting strain of β-hemolytic streptococcus, (*5*) variations in the ability of the host to respond, and (*6*) the severity and nature of the infectious process.

In the present study an attempt was made to control the first three factors. A quantitative method (5) for the determination of antifibrinolysin antibodies was employed; antibody titers were determined on acute and convalescent sera at the

same time. Under these conditions an increase in either antistreptolysin or antifibrinolysin titer of two dilution increments was considered significant and beyond the error of the test (10, 5).

In order to identify streptococcal infections accurately, each subject admitted to the hospital was examined daily, multiple cultures of the throat were taken, and acute-phase and usually several convalescent-phase blood specimens were obtained.

It has been demonstrated (11) that antifibrinolytic properties may not develop until the second to fourth week of convalescence. With few exceptions, therefore, one or more serum specimens were taken during the third to sixth week following the initial bleeding.

Since it has been shown previously that bacteriological and clinical evidence alone is not necessarily sufficient to establish an etiological diagnosis (12), antistreptolysin as well as antifibrinolysin determinations were made on all sera collected. It was therefore possible to study the frequency and specificity of the antifibrinolysin response from the standpoint of the clinical diagnosis, the presence or absence of β-hemolytic streptococci obtained from cultures of the throat, and the antistreptolysin response.

Source of cases

The respiratory illnesses include (*1*) 116 consecutive hospitalized cases of sporadic exudative tonsillitis and pharyngitis studied in the spring of 1943 (12), (*2*) 100 cases of tonsillitis and pharyngitis resulting from a foodborne epidemic in November 1943 (13), and (*3*) 525 cases admitted to the respiratory wards in the winter and spring of 1944. Each subject was bled at the time of admission to the hospital, and one or more convalescent blood specimens were taken from 1 to 6 weeks later. On most hospitalized soldiers swab cultures of the throat were made on at least 3 successive days after admission. The clinical diagnosis was made from the history, daily physical examination, and roentgenogram of the chest.

The antifibrinolysin response in hospitalized soldiers with presumptive streptococcal infections is shown in Table III. Included in the table are 232 patients who were found to have exudate on the tonsils or pharynx and from whom the β-hemolytic streptococcus was isolated during the first 3 days of hospitalization. There were 151 in the group, or 65 per cent, who not only had clinical and bacteriological evidence of streptococcal infection, but also responded by an increase in antistreptolysin antibodies. This group of 151 men was considered to have had *proved* infections caused by the β-hemolytic streptococcus. The antifibrinolysin titer was found to increase significantly in only 56, or 37 per cent of these patients. This indicated that the antifibrinolysin response was not as sensitive an index of streptococcal infection as the antistreptolysin response.

TABLE III

Antifibrinolysin and antistreptolysin response in 232 patients with exudative tonsillitis or pharyngitis from whom β-hemolytic streptococci were isolated

Antistreptolysin response	Antifibrinolysin response		Totals	Antifibrinolysin response
	number positive	*number negative*		*per cent positive*
Number positive	56	95	151	37
Number negative	12	69	81	15
Totals	68	164	232	29

Definition: A difference in titer of antistreptolysin or antifibrinolysin of two succesive tube dilutions between the acute-phase and convalescent-phase sera was considered a positive test.

Since it has been demonstrated that antistreptolysin antibodies increase significantly in only 85 per cent of probable streptococcal infections, scarlet fever (10) and epidemic foodborne septic sore throat (13), it was of considerable importance to determine the frequency with which antifibrinolysin responses occurred in the absence of an increase in antistreptolysin antibodies. There were 81 patients with exudative tonsillitis harboring β-hemolytic streptococci who failed to respond to the infection by an increase in antistreptolysin titer. Twelve of these patients, or 15 per cent, exhibited an increase in antifibrinolysin antibodies.

Significant increases in both antifibrinolysin and antistreptolysin antibodies were less frequent in subjects with respiratory disease from whom β-hemolytic streptococci were isolated, but in whom no exudate was present on the lymphoid tissues of the throat. In 140 such patients (Table IV), 41, or 27 per cent, exhibited an increase in antistreptolysin antibodies, and 21, or 15 per cent, developed antifibrinolysin antibodies. Among patients without an antistreptolysin response, only 7 per cent developed an increase in antifibrinolysin antibodies.

TABLE IV

Antifibrinolysin and antistreptolysin response in 140 patients with respiratory disease other than exudative tonsillitis and from whom β-hemolytic streptococci were isolated

Antistreptolysin response	Antifibrinolysin response		Totals	Antifibrinolysin response
	number positive	*number negative*		*per cent positive*
Number positive	14	27	41	34
Number negative	7	92	99	7
Totals	21	79	140	15

Specificity of the antifibrinolysin response

The data presented in Tables III and IV, show, therefore, that antifibrinolysin antibodies increased following clinical infection with the β-hemolytic streptococcus. Further studies of the specificity of the reaction were then carried out.

Of 404 well soldiers, antifibrinolysin and antistreptolysin antibodies were determined on sera collected from 390. The change in titer between the initial serum specimen and a subsequent sample collected 21 to 60 days later is presented in Table V according to the presence or absence of β-hemolytic streptococci during the period of study. Those subjects who never carried β-hemolytic streptococci did not show an increase in either antibody. Seventeen of the men who were carriers of the β-hemolytic streptococcus showed an increase in antistreptolysin antibodies and one developed antifibrinolysin antibodies. These data demonstrate that an increase in titer of either antibody in the absence of β-hemolytic streptococci was not observed. Carriers, however, may occasionally show an increase in antistreptolysin antibodies but rarely an increase in antifibrinolysin titer.

TABLE V

Antifibrinolysin response in 390 well soldiers according to the presence or absence of β-hemolytic streptococcus in the oropharynx and the antistreptolysin response

Antistreptolysin response	β-hemolytic streptococcus			
	Present		Absent	
	Antifibrinolysin response		Antifibrinolysin response	
	number positive	*number negative*	*number positive*	*number negative*
Number positive	0	17	0	0
Number negative	1	136	0	236

The antibody response to non-specific infections was studied in 244 sets of sera obtained from soldiers hospitalized for respiratory disease. The diagnoses included 200 cases of acute undifferentiated respiratory disease, 19 patients with atypical pneumonia, and 25 cases of a miscellaneous group including penumococcal pneumonia, pulmonary tuberculosis, sinusitis, and influenza A. No instance of exudative tonsillitis or pharyngitis was included, nor in any case, were β-hemolytic streptococci isolated from the throat during the first 3 days of hospitalization.

Of the 244 sets of sera examined, 232 convalescent sera did not exhibit an increase in either antifibrinolysin or antistreptolysin antibodies (Table VI). In 12 patients the antistreptolysin titer of the convalescent serum was significantly increased over the acute phase specimen. In 3 of these patients there was also an increase in antifibrinolysin antibodies. These results demonstrated, therefore, the high degree of specificity of the antifibrinolysin test, in that in only 3 instances was an increase in antibodies demonstrated in the absence of clinical and bacteriological evidence of streptococcal infection, and in each of the 3 sets of sera a concomitant increase in antistreptolysin titer was observed.

TABLE VI

Antifibrinolysin and antistreptolysin response in 244 hospitalized soldiers with respiratory disease other than exudative tonsillitis and from whom no β-hemolytic streptococci were isolated

Antistreptolysin response	Antifibrinolysin response		Totals	Antifibrinolysin response
	number positive	*number negative*		*per cent positive*
Number positive	3	9	12	25
Number negative	0	232	232	0

The question of the specificity of the antistreptolysin response observed in this group of patients cannot be answered. It is to be emphasized, however, that bacteriological data were obtained only during the first 3 days of hospitalization, so that hospital cross infection, or inapparent infections in the field may have occurred prior to the time the convalescent blood was taken.

The only instances of an antifibrinolysin re-

sponse in the absence of either bacteriological or serological confirmation of the streptococcus etiology occurred in a group of 115 soldiers hospitalized for exudative tonsillitis from whom no β-hemolytic streptococci were isolated. In 4 of these patients the titer of antifibrinolysin increased during convalescence without a concomitant increase in the antistreptolysin titer. The sera from these 4 patients had been stored 16 months prior to the determination, and they were known to be contaminated. Whether they represent true instances of non-specific antifibrinolysin reactions cannot be determined.

DISCUSSION

According to the review of Tillett (8) 85 to 90 per cent of plasma collected from normal individuals was found to contain little or no antifibrinolysin as indicated by the lysis of such plasma clots within one hour. The results obtained by different investigators (8) are in general agreement, in spite of the fact that the amount or source of fibrinolysin used was not standardized. In the present study the fibrinolysin was obtained from a group A strain of β-hemolytic streptococcus, and in all tests a standard unit of fibrinolysin was employed. Under these conditions a titer of 50 units or less was exhibited by 66 per cent of sera collected from normal subjects, indicating the presence of little or no antifibrinolysin. In approximately 11 per cent of the normal subjects the antifibrinolysin antibodies were considered to be elevated in that the titer was greater than 150 units. Normal individuals found to harbor group A β-hemolytic streptococci in the oropharynx showed a slightly different distribution of the antifibrinolysin titers with 15 per cent greater than 150 units.

That the high antifibrinolysin titers observed in normal subjects resulted from previous experience with the β-hemolytic streptococcus was indicated by the fact that the antistreptolysin titer was usually elevated in those sera which also showed a high antifibrinolysin titer. However, it was also noted that elevated antistreptolysin titers are not always associated with a high antifibrinolysin titer, in fact, in only 20 per cent of sera whose antistreptolysin titer was 159 or greater was the antifibrinolysin titer greater than 150 units. These results would indicate then, that streptococcal infections produce an antistreptolysin response more frequently than an antifibrinolysin response. This was confirmed when the antibody response was studied in 232 hospitalized soldiers with exudative tonsillitis or pharyngitis from whom β-hemolytic streptococci were isolated from the throat cultures. Of this group, 151 showed an increase in antistreptolysin antibodies, whereas in only 68 was there an increase in the antifibrinolysin titer. As a routine diagnostic test, therefore, the demonstration of an increase in antistreptolysin titer is a more sensitive index of streptococcal infection than an increase in antifibrinolysin antibodies.

Since not all patients with streptococcal infections exhibit an increase in antistreptolysin during convalescence, the additional determination of antifibrinolysin antibodies has proved valuable. Approximately 15 to 20 per cent of patients with scarlet fever (10) or epidemic exudative tonsillitis (13) fail to develop antistreptolysin during the convalescent period, and yet there is little doubt that the infection was caused by the β-hemolytic streptococcus. In a recent study of a food-borne epidemic of exudative tonsillitis and pharyngitis caused by a type 5 β-hemolytic streptococcus, 80 of 100 patients showed a significant antistreptolysin response (13). Of the entire group, 20 showed an increase in antifibrinolysin antibodies, 4 of which occurred in patients who showed no significant change in the antistreptolysin titer. The serological response in 232 soldiers with exudative tonsillitis from whom β-hemolytic streptococci were isolated show that 12 individuals, or 5 per cent, exhibited an increase in antifibrinolysin titer without a concomitant increase in antistreptolysin.

The data in the present report demonstrate that an increase in titer of two dilution increments during convalescence is highly specific. A total of 98 individuals showed an increase in antifibrinolysin antibodies, in 70 of whom there was both bacteriological and serological (antistreptolysin) evidence of streptococcal infection. In 20 there was only bacteriological evidence, and in 4 only serological indication of the streptococcal etiology. In 4 cases of exudative tonsillitis the development of antifibrinolysin antibodies was the only evidence of infection caused by the β-hemolytic streptococcus.

In contrast to the studies reviewed by Tillett (8) which showed that 67 per cent of patients with

streptococcal tonsillitis develop antifibrinolysin antibodies during convalescence, is the fact that only 37 per cent of the present series of patients with streptococcal infections of the throat, as proved by an increase of antistreptolysin, showed an increase in the antifibrinolysin titer. The cause for these differences was not at once apparent. The lack of adequate convalescent serum specimens does not explain the low incidence of antifibrinolytic responses observed in this study, since one or more sera obtained 3 to 6 weeks after the initial bleedings were tested in almost every instance. Although the majority of the patients with *proved* streptococcal infections reported in this study were only mildly ill, there were no obvious differences in the severity of illness of those patients who did or did not exhibit an increase in the antifibrinolytic titer.

Recently it has been demonstrated that the different types of streptococci vary in their capacity to produce erythrogenic toxin as measured by the incidence of scarlet fever (14). Similarly, some evidence was obtained in this laboratory that different strains of streptococci varied in their ability to stimulate antistreptolysin formation (12). These observations suggested that β-hemolytic streptococci may vary in their ability to produce an antifibrinolytic response.

Extensive clinical and laboratory studies were therefore undertaken to determine the factors which are responsible for the stimulation or lack of stimulation of antifibrinolysin. A preliminary report of these investigations presented elsewhere (5) demonstrated that the increase in antifibrinolysin titer during convalescence was dependent on the strain of group A streptococcus responsible for the infection. Endemic infections caused by type 3 streptococci resulted in few antifibrinolytic responses (10 per cent), whereas 62 per cent of infections due to type 19 showed an increase in antifibrinolysin. Likewise, types 5 and 12 streptococci producing epidemic sore throat showed marked differences in their ability to stimulate antibody formation, with 20 and 92 per cent respectively of the patients exhibiting an increase in the antifibrinolysin titer. The amount of fibrinolysin produced by these streptococci was measured, and it was found that, in general, organisms which stimulate antifibrinolysin formation *in vivo,* produced large amounts *in vitro,* while those streptococci that produced small amounts of fibrinolysin generally failed to stimulate antibody formation.

SUMMARY

Quantitative antifibrinolysin estimations were made of sera collected from 1204 subjects. Analysis of the data thus obtained showed that sera from the majority of normal subjects contain little antifibrinolysin. In approximately 12 per cent of normal individuals, the titer was elevated above 150 units, presumably due to previous experience with the β-hemolytic streptococcus.

An increase in the antifibrinolysin titer of two dilution increments was shown to be indicative of a previous infection by the β-hemolytic streptococcus. Antifibrinolysin developed in 29 per cent of patients with exudative tonsillitis from whom β-hemolytic streptococci were cultured, whereas antistreptolysin increased in 65 per cent.

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