STUDIES OF HEMOLYTIC STREPTOCOCCAL INFECTION

II. THE SEROLOGICAL REACTIONS OF THE BLOOD DURING ERYSIPELAS [1]

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As a part of an investigation of the various serological reactions that occur during and after hemolytic streptococcal infections, we have studied 30 patients with erysipelas. In a previous paper (1), various important factors in the epidemiology, prognosis and course of the disease in patients with erysipelas were discussed. At this time, we present information obtained from a study of the antistreptolysin (antihemolysin), antifibrinolysin and the streptococcidal power of whole defibrinated blood. In addition, the complement of the blood serum was titrated, agglutination reactions against the organism derived from the patient, and skin reactions to "Dick" toxin and streptococcal nucleoprotein were investigated.

METHODS OF STUDY

All of the patients were studied while they were under observation in the Boston City Hospital. After their illness had subsided and after discharge from the hospital they were followed for periods of one to eight months. *B. hemolytic streptococci* were isolated from all of the patients. When it was not possible to obtain the organisms directly from the lesion, they could be obtained from the nasal secretions. It was of interest from the standpoint of the mode of invasion and pathogenesis of the infection that many of the patients with erysipelas unassociated with a wound had had a preceding acute follicular tonsillitis or an acute rhinitis from which *B. hemolytic streptococci* could be isolated with regularity. This is in agreement with the studies of Holmes (2).

Antistreptolysin. The antistreptolysin titer of the blood serum of the patients was determined by the method of Todd (3) and examinations were carried out in the same manner as that recorded in our previous studies (4) of patients with rheumatic fever and rheumatoid arthritis. The results are expressed in units, a unit being the amount necessary to inactivate 0.5 cc. of a streptolysin solution of such potency that 0.2 cc. would completely hemolyze 0.5 cc. of a 5 per cent suspension of washed sheep cells in normal saline solution. A serum was recorded as containing 100 units per cc. when 1 cc. of the 1 : 100 dilution was the least amount necessary to inactivate 0.5 cc. of standard streptolysin solution.

Antifibrinolysin. The method of Tillett and Garner (5) was used in performing this test. The organism that we used for the production of fibrinolysin was the same (CO) as that we have employed previously (6). The results were recorded in degrees of resistance according to the classification suggested by Tillett, Edwards and Garner (7). Control samples of blood plasma were tested every day, and complete dissolution of the plasma clot in all of our control patients took place in less than one hour.

Streptococcidal power. The streptococcidal action was studied in the whole defibrinated blood by the method of Todd, as employed by Ward (8) and Finland and Sutliff (9) in studying the pneumococcus. Different dilutions of an 18-hour broth culture of the hemolytic streptococcus were added to 0.5 cc. of defibrinated blood in a small pyrex tube. The tubes were sealed in a gas-oxygen flame and placed in a machine which rotated the tubes end to end within the incubator for 24 hours. At the end of that time the tubes were opened, and cultures were made to determine which tubes continued to contain live organisms. The number of organisms in the various dilutions was determined by plating 1 cc. of the dilutions of 10^{-6}, 10^{-7} and 10^{-8}. As a rule, in the 10^{-7} dilution there were from eight to 24 organisms.

As controls, the patient's own organism was

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mixed with the whole defibrinated blood of an individual without streptococcus infection; the blood from the same individual was used each time the test was done.

In addition to studying the killing power of whole blood by means of the patient's own organism, another virulent strain of hemolytic streptococcus, obtained from a case of meningitis, was used repeatedly in each case. The purpose of this was to determine whether the killing power of blood of patients with erysipelas was the same or different for their own strains of streptococci and a strain of streptococcus isolated from an individual suffering from a streptococcal infection other than erysipelas.

The same procedure was carried out with the controls. The results are recorded in accordance with the maximum number of organisms killed by 0.5 cc. of blood. That is to say, if there was growth in the tube containing 0.1 cc. of a 10^{-1} dilution and none in the tube containing 0.1 cc. of the 10^{-2} dilution, it was recorded—killing power in 10^{-2}.

Skin tests. The ability of the patient's skin to react to one skin test dose of Dick toxin and to 0.01 mgm. of nucleoprotein derived from a strain of hemolytic streptococcus (NY5) was tested. A reaction, 1 cm. in diameter, was considered positive.

Complement. The titer of the complement of the patient's blood serum was determined at different times during the course of the disease. This was done by adding different amounts of the patient's blood serum to 0.5 cc. of sensitized sheep cells and placing the mixture in the water bath at 37° C. for one hour. The smallest amount of serum which was required to effect complete hemolysis of 0.5 cc. of sensitized sheep cells was taken as the amount of complement present.

Sensitized sheep cells were prepared by mixing equal quantities of diluted amboceptor and a 5 per cent suspension of washed sheep cells and placing the mixture in the water bath at 37° C. for thirty minutes.

The stock amboceptor that was used in these tests was diluted in accordance with its potency which had been determined by means of previous titrations against sheep cells and complement. In all of the tests reported, 0.1 cc. of the stock amboceptor was diluted to 25 cc. with physiological salt solution, and used on the same day.

Agglutination tests. Agglutination tests were done with the organism obtained from the patient and with the NY5 strain of a hemolytic streptococcus. All tests were carried out with organisms that had been killed at 56° C. in accordance with the technique previously described (10).

RESULTS

Antistreptolysin. Isolated observations showed that the antistreptolysin titer of the blood serum of patients with erysipelas varied from 80 to 10,000 units. This is in accord with our previous observations (4) in patients with erysipelas. Of greater importance than isolated observations were the changes in the titer that occurred during the course and following the recovery from the disease. In no case did we fail to observe an increase in the antistreptolysin titer of the blood serum as the disease progressed. The magnitude of the increase is illustrated in Figure 1. In some the amount of increase was slight, in others it was considerable. When the serum of individual patients was tested repeatedly over a considerable period of time, it was found that the titer of the antistreptolysin not only increased during the course of the disease but that it frequently remained elevated above the original determination for some weeks or months after the acute infection subsided. The highest titer was usually reached within the first 20 days after the onset of the illness, and, in most cases, it was obtained by the 10th to the 15th day. In no case did we observe an increase in the titer after the 20th day. Once the peak had been reached, increases in the titer were not observed unless there was a reinfection such as a recurrence of the erysipelas. The titer of the serum remained above the level of the first observation for periods varying from 40 days to six months. The titer of the antistreptolysin content of the serum at various times during and after the infection is charted in Figure 2. In all of the cases in which the titer remained above 1,000 units after the 20th day of the disease, there were suppurative complications due to the hemolytic streptococcus. Moreover, the patients who had 500 or more units before the 10th day invariably gave a history of hemolytic strep-

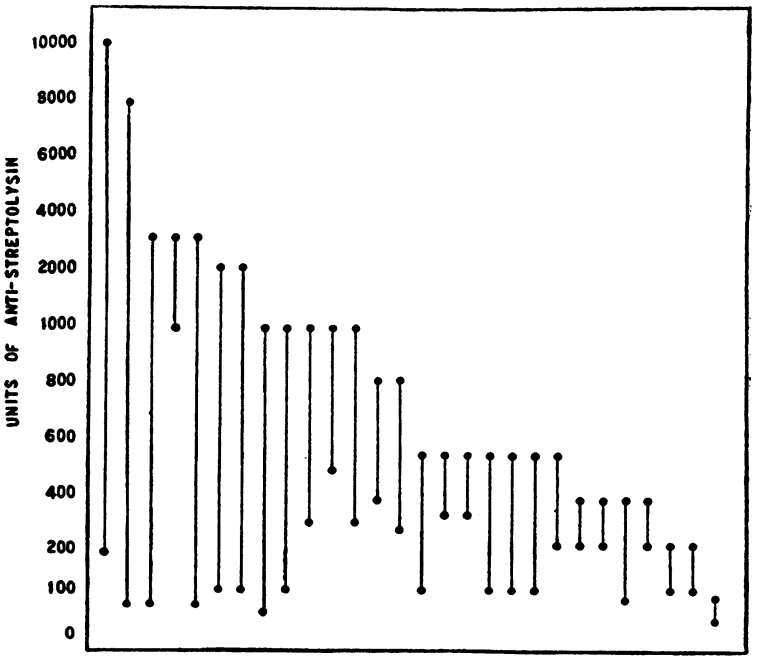

FIG. 1. THE ANTISTREPTOLYSIN IN PATIENTS WITH ERYSIPELAS

Each pair of dots represents the lowest and highest antistreptolysin content of the blood observed during the course of the disease.

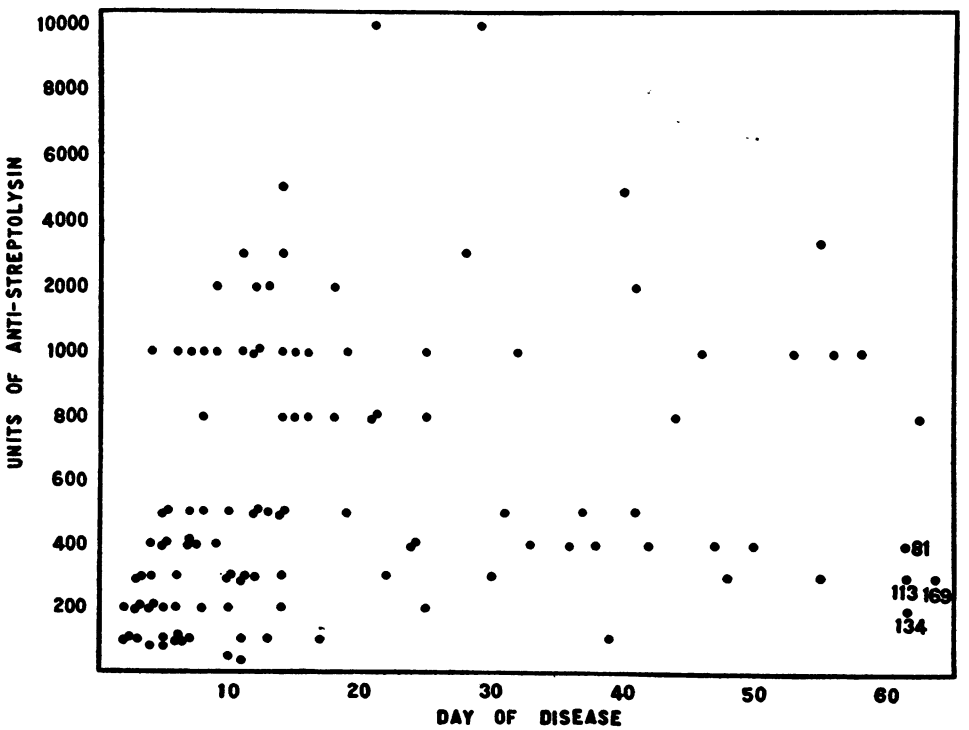

FIG. 2. THE ANTISTREPTOLYSIN TITER AND THE DAY OF THE DISEASE

Each dot represents the antistreptolysin content of a specimen of blood serum.

tococcus infection before the onset of the erysipelas.

Antifibrinolysin. Of the 30 patients studied in this series of cases, 24 developed maximum resistance to fibrinolysin. The results obtained were in general agreement with our previous observations of this test in erysipelas, and are in accord with the results recorded by Tillett (11). Our results in 55 cases are recorded in Table I.

TABLE I

Results of resistance to fibrinolysin of hemolytic streptococcus

Number of cases	Maximum resistance. No dissolution in 24 hours ++++	High resistance. Dissolution in 8 to 24 hours +++	Dissolution in 3 to 8 hours ++	Dissolution in 1 to 3 hours +	No resistance. Dissolution in less than 1 hour −
Present series 30	24	1	3	2	0
Previous series 25	22	0	2	1	
55	46	1	5	3	

In the present group of 30 patients, 15 showed maximum resistance to fibrinolysis of their coagulated plasma when they were first seen. Nine patients, who showed no resistance when they were first admitted, developed it during observation, whereas the remaining six individuals never developed maximum resistance. Once it appeared, it persisted for periods of time varying from 8 to 150 days. In the patients who did not show resistance to fibrinolysis when they were first seen, the day of the disease varied from the second to the ninth day, and resistance appeared between the fifth and 14th day. If no demonstrable resistance was present at the onset of the erysipelas, we failed to observe the development of complete resistance before the fifth day of the disease.

The 15 patients showing maximum resistance when they were first examined require comment. These individuals were seen from the second to the eighth day of their illness. In five of them, there would have been ample time for the development of resistance, as judged from the study of individuals who were seen early in the course of the illness. In the other 10 cases, which showed maximum resistance before the fifth day of the attack of erysipelas, the presence of an active hemolytic streptococcal infection of the throat and nasopharynx prior to the onset of erysipelas was the most likely explanation for the presence of antifibrinolysin. This conclusion received support from their clinical history. It was of further interest that erysipelas could occur in spite of the presence of maximum resistance to fibrinolysis. This fact is emphasized by the observation of the presence of resistance at the onset of recurrences of erysipelas. We also have observed cases in which resistance to fibrinolysin had disappeared and then reappeared following a recurrence of a streptococcal infection. It seems evident, then, that resistance to fibrinolysin is a response to a hemolytic streptococcal infection, and once it becomes established it may persist for periods of time varying from eight to 150 days.

STREPTOCOCCIDAL POWER OF THE WHOLE DEFIBRINATED BLOOD

1. *Controls: Patient's organism and whole defibrinated blood of controls.* One-half a cubic centimeter of a normal individual's whole defibrinated blood was mixed with different dilutions of a 24-hour broth culture of the hemolytic streptococcus isolated from the patient and incubated as described under methods of study. The same individual was used as a control every time the patient's blood was studied, and in this way the results could be compared. It was found that the streptococcidal power of the blood of the controls did not vary more than a dilution found in two tubes, i.e. 100-fold dilution when the number of organisms in the dilutions was controlled. For this reason, we believed that variations in the streptococcidal power of the patient's blood would have to be greater than the dilution of two tubes in order to be of significance. In other words, an increase greater than 100 times the killing power of the first observation was necessary before we considered that the patient showed a significant increase in his streptococcidal power. In case there was no evidence of an increase of streptococcidal power as defined above, we considered that the patient had a higher streptococcidal power than the control if his blood were able to kill more than 100 times as many organisms at any time during the period of observations.

When the standards described above were used,

it was found that there was considerable variation in the killing power of the blood of the controls when the different organisms were used. The maximum number of organisms killed by the blood of the controls during the period of observation is shown in Column B of Figure 3.

of the increase in streptococcidal power during the course of the disease and the maximum number of organisms killed. When the results were studied to determine the difference in the streptococcidal power of the blood in the patients and in the controls, it was found that eight patients

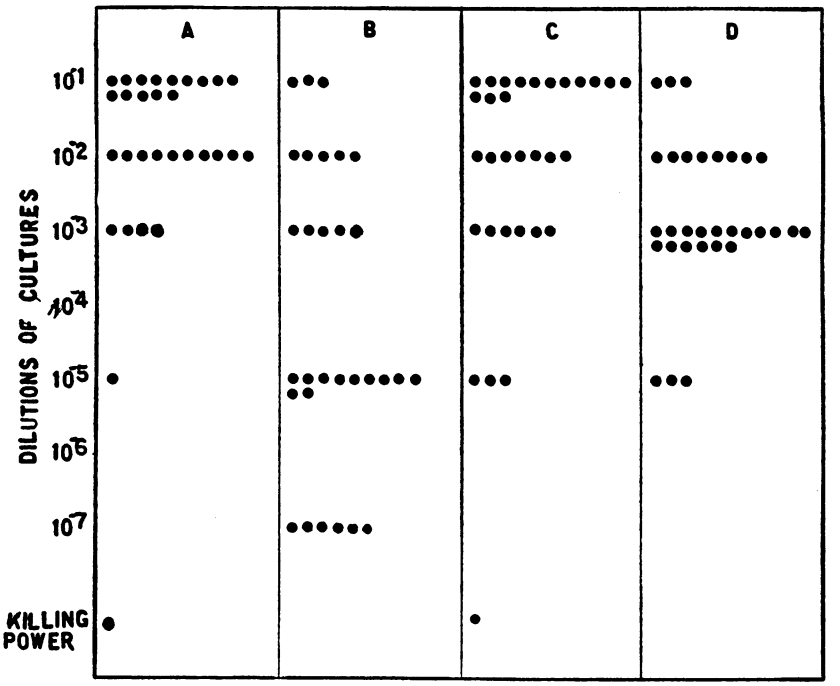

FIG. 3. THE MAXIMUM STREPTOCOCCIDAL POWER IN PATIENTS AND CONTROLS

Each dot in Column A represents the maximum streptococcidal power of a specimen of whole blood against the patient's own organism. Each dot in Column B represents the maximum streptococcidal power of whole blood in controls against the patient's organism. Each dot in Column C represents the maximum streptococcidal power of a specimen of whole blood from patients with erysipelas against another strain of hemolytic streptococcus derived from a non-erysipelas infection. Each dot in Column D represents the maximum streptococcidal power of a specimen of whole blood from control individuals using the same strain as in Column C.

2. Patient's own organism against patient's whole defibrinated blood. When the streptococcidal power of the patients' blood was studied, it was found that they were able to kill varying numbers of their own organisms. Column A of Figure 3 shows the maximum number of organisms killed by the patient's own blood and Column B the maximum number killed by the controls. In Figure 4, the change in the streptococcidal power on repeated examinations is charted. Generally speaking, the patients showed greater streptococcidal power than the controls; this was true

showed more than a 100-fold increase in their streptococcidal power, 13 a 10-fold to a 100-fold increase, and eight no change. Upon the remaining patient only one observation was made. The increases in streptococcidal power were observed from the 8th to the 81st day of the disease and did not coincide with the recovery of the patient. From these observations it was plain that during the course of the disease it could be shown that the streptococcidal power of the whole blood of some individuals increased considerably, while in others the changes were less striking.

Despite the fact that a number of patients failed to show very significant increases in streptococcidal power during the period of observation, it was noted repeatedly that the patients had a higher streptococcidal power than the controls. Thirteen of them were able at all times to kill from 1,000 to 10,000 times as many organisms as the controls, 10 killed 100 times as many or less, five the same number as the control and, in one, the control was better than the patient. That is to say, in some patients there was an actual increase in the whole blood killing power of the patients' blood during the course of the disease; in other cases, there was evidence that the streptococcidal power of the patients' blood was greater than the controls although no striking increase was noted during the period of observation.

These observations indicate that the killing power of whole blood of patients with erysipelas is frequently increased above that of controls, and that the increase in the killing power is most likely due to the presence of an active hemolytic streptococcal infection.

Whole defibrinated blood of patients and controls and an organism derived from streptococcal meningitis. In addition to studying the streptococcidal power of the blood with organisms derived from the patients, another strain of hemolytic streptococcus was obtained from a case of streptococcal meningitis and studied in connection with the blood of patients with erysipelas and controls. The maximum killing power of the blood serum in each case is recorded in Figure 3. Column C represents the results in patients with erysipelas and Column D, the results in the controls. By and large, the patients with erysipelas showed somewhat greater streptococcidal power for this organism than the controls. It is to be noted, however, that the different controls possessed some streptococcidal power against this particular strain of hemolytic streptococcus, indicating that the ability to kill certain strains of

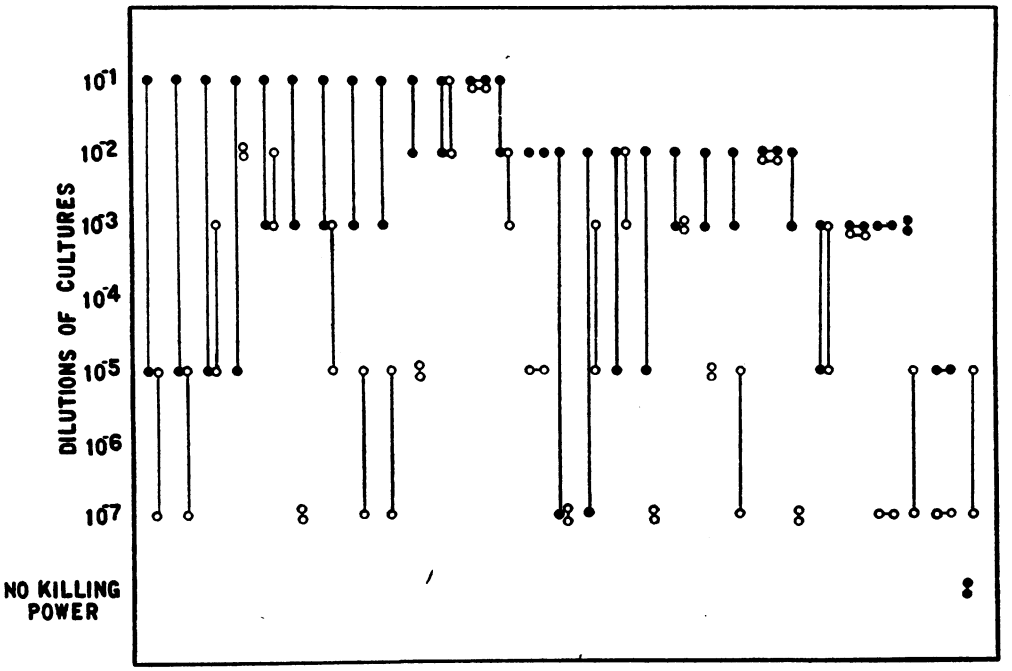

FIG. 4. THE MAXIMUM AND MINIMUM STREPTOCOCCIDAL POWER OF THE WHOLE BLOOD IN PATIENTS AND CONTROLS

Each pair of solid dots represent the maximum and minimum streptococcidal power of the blood in patients with erysipelas using the organism derived from the patient. Each pair of circles represent the same determination in controls.

hemolytic streptococci is possessed by some normal individuals without infection.

Results of complement titration. Since it is generally believed that complement contributes to the intracellular destruction of organisms by rendering them susceptible to phagocytosis, it was titrated in the blood serum of the patients studied by us. The purpose of this was to determine whether there was any correlation between the killing power of whole blood and the amount of complement present in it and, secondly, whether there were any consistent changes during the course of the disease. The results have been charted in Figure 5.

It was not possible to demonstrate any definite correlation between the amount of complement and the streptococcidal power of the whole defibrinated blood. From these observations, it would appear that in most cases at least there was sufficient complement present in cases of erysipelas to render the organisms susceptible to phagocytosis.

The fluctuations of complement during the course of the disease proved of interest. It has been stated that the complement of normal noninfected individuals fluctuates only slightly between 0.03 and 0.06 cc. This is not in agreement with our observations. We have found wide variations in different individuals when the titrations are done repeatedly. Figure 6 illustrates the variation of the titer in four individuals whose blood was titrated repeatedly over a period of from one to two years. While these individuals did not show fluctuations of more than 0.1 cc. on repeated examinations, it is obvious that normal individuals may show great differences in the amount of complement present. This must be taken into account in any interpretation of complement titers.

During the course of erysipelas, the titer of the

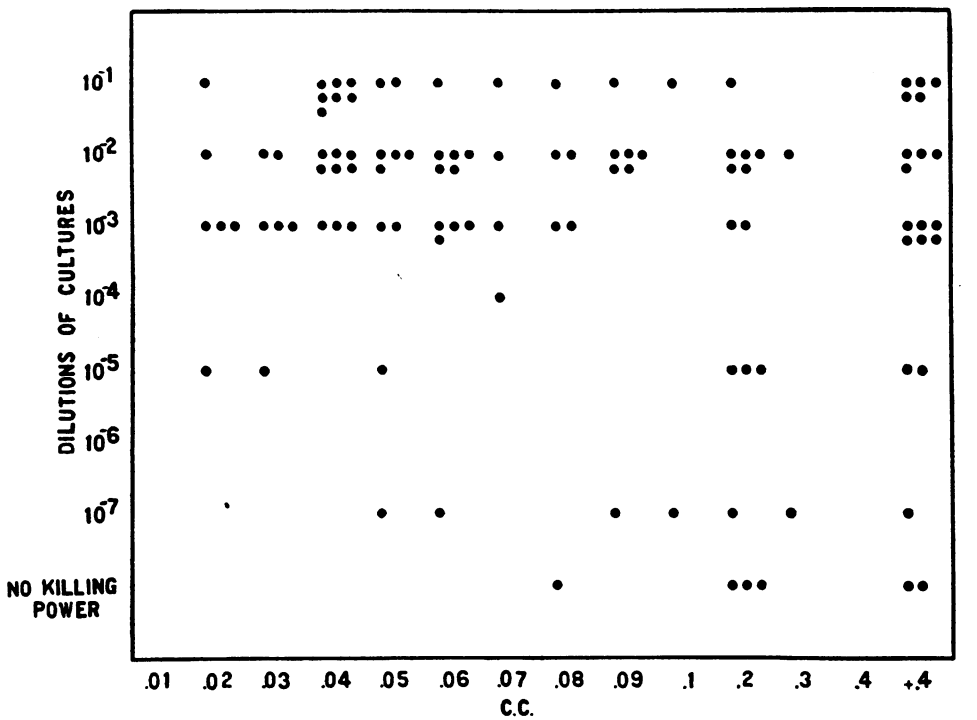

FIG. 5. THE STREPTOCOCCIDAL POWER OF THE WHOLE BLOOD AND THE COMPLEMENT TITER OF THE BLOOD SERUM

Each dot represents the streptococcidal power of a specimen of whole blood and the complement titer of the blood serum from the same individual.

complement in patients with erysipelas decreased more than 0.1 cc. in nine, increased more than 0.1 cc. in five and remained the same in 16. From these observations it can be concluded that during the course of erysipelas the complement of some patients may fluctuate in greater amounts than is seen in controls without infection. In our experience, however, sharp increases or decreases as indicated by the titration could not be correlated with an improvement or an exacerbation of the infection. The magnitude of the fluctuations observed in infected individuals is shown in Figure 7.

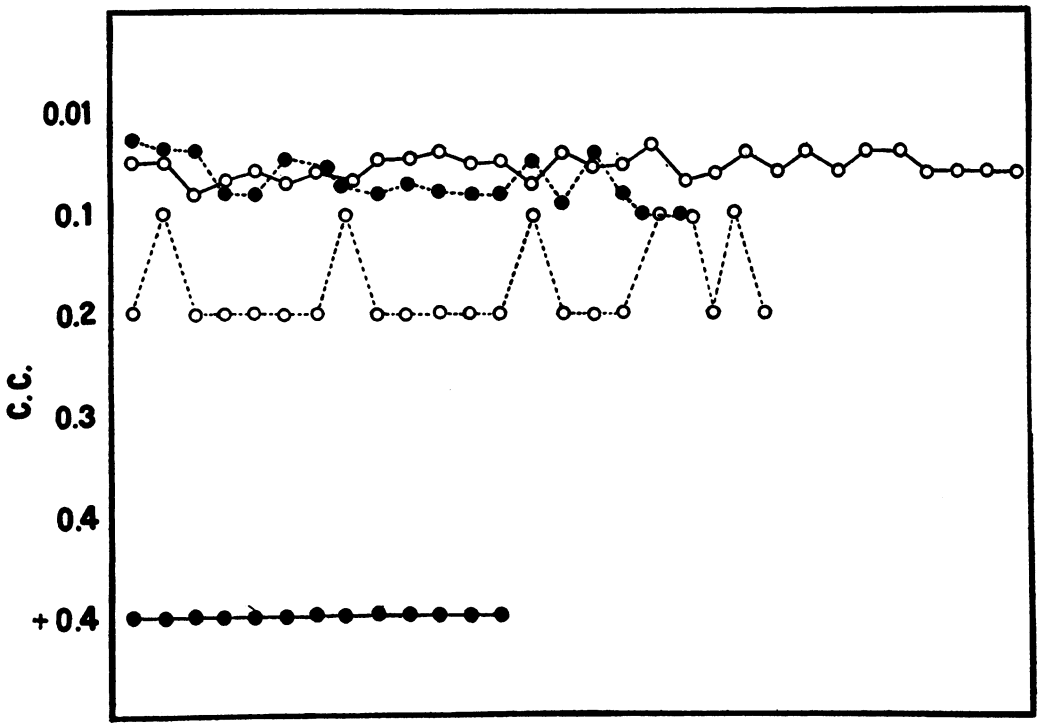

FIG. 6. THE VARIATIONS IN COMPLEMENT TITER IN NORMAL INDIVIDUALS

Each line indicates the fluctuation of the complement titer in a normal individual followed over a period varying from one to two years.

Agglutination tests. The blood serum from patients with erysipelas was tested for agglutinins against their own organisms at various intervals during and after the course of the disease. In addition to using the patient's own organism, the NY5 strain of hemolytic streptococcus was used as an agglutinogen. Only three of 30 patients showed agglutinins against their own organisms in dilutions varying from 1 to 40 to 1 to 80, while six agglutinated NY5. In two patients showing the highest titers there were suppurative complications. From these observations, it is possible to state that in our experience at least, agglutinins appear in the serum irregularly and the titer is not high. This is precisely what we (10) found in previous observations.

Skin tests. Results of Dick test. Only one of the 30 patients showed a positive skin reaction following the injection of one skin test dose of "Dick" toxin into the skin. The others yielded negative results. When the nucleoprotein derived from the *Streptococcus scarlatinae* was used, it was found that 24 reacted in a positive manner and six were negative. Of the 24 who reacted, 20 of them showed a positive reaction to 0.01 cc. when first tested, while four more showed positive reactions to a second injection of the same material given five to seven days after the first.

DISCUSSION

From the data presented there is considerable evidence that during and following erysipelas there is an increase in the antistreptolysin and antifibrinolysin of the blood. In addition, in about one-third of the cases, the streptococcidal power of the whole blood increases. While there is no precise relation between the time of recovery and the demonstration of increasing amounts of these antibodies in the blood, there seems to be little doubt that their presence indicates a response on the part of the host to the streptococcal infection.

unless rendered susceptible by the presence of antibacterial substances. Moreover, it can be demonstrated that these different special properties call forth specific immunological responses which are independent of one another. It was for these reasons we studied the different kinds of response simultaneously.

In view of the multiple serological reactions that can be demonstrated in patients with hemolytic streptococcal infection, it is naturally difficult to decide whether one response is more important than another in bringing about recovery. Recovery probably results from a summation of a variety

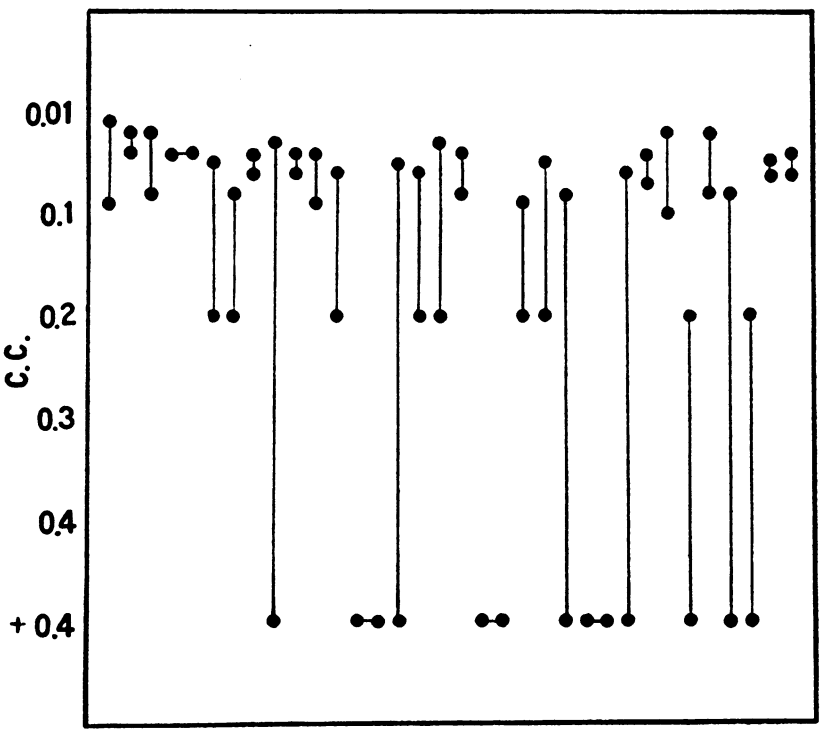

FIG. 7. THE MAXIMUM AND MINIMUM AMOUNTS OF COMPLEMENT
Each pair of dots represents the maximum and minimum amounts of complement observed during the course of the disease.

The complement was present in varying amounts and, in most cases, seemed to be adequate for the phagocytosis of streptococci as indicated by the streptococcidal test.

From a consideration of the results of numerous investigations, it is generally believed that hemolytic streptococci are capable of elaborating toxins, hemolysins, leukocidins and fibrinolytic substances. In addition, they resist phagocytosis

of processes which are capable of keeping the infectious process localized and destroying or limiting the growth of the organisms in the tissues. Of all these reactions, the presence of antibodies that aid in the phagocytosis and destruction of the organism would seem to be of the greatest importance.

Recent investigations by Hare (12) of hemolytic streptococcal infections, especially those oc-

curring in the puerperium, are significant. Since these infections are commonly localized in one small area, that is, the uterus and its immediate neighborhood, the results he obtained from the study of the bactericidal power of the blood during this type of infection were of interest in the light of the present investigation of erysipelas. In Hare's experience, the patients with hemolytic streptococcal infections in which the process was localized to the uterus or its immediate neighborhood, showed a normal bactericidal power of the blood early in the course of the disease. There was a tendency in some cases for this to increase, but it was not a constant finding so that he believes that it was doubtful whether the absence of more widespread invasion was due to a high degree of general immunity. In the patients with generalized infection who recovered, the bactericidal power of the blood was much greater than normal, and in patients with generalized infection who died, the bactericidal power was greater than normal in about one half the cases. Hare's results are in general agreement with our observations in patients with erysipelas and other streptococcal infections. That is to say, in some patients with a localized infection, recovery may occur without any demonstrable increase in the bactericidal power of the blood. In other patients, an increase in general resistance was shown, and this occurred even in the presence of invasion of the blood stream.

Two types of response that may be observed in patients with erysipelas are illustrated by Figures 8 and 9. The various observations made in Case 2 are charted in Figure 8. During the course and following the illness in this case there was an increase in the titer of antistreptolysin, antifibrinolysin and the killing power of whole blood. Agglutinins appeared in several patients, especially in the presence of suppurative complications. It was striking that the increased streptococcidal power and the antistreptolysin persisted for a period of six months, whereas the antifibrinolysin diminished after 22 days.

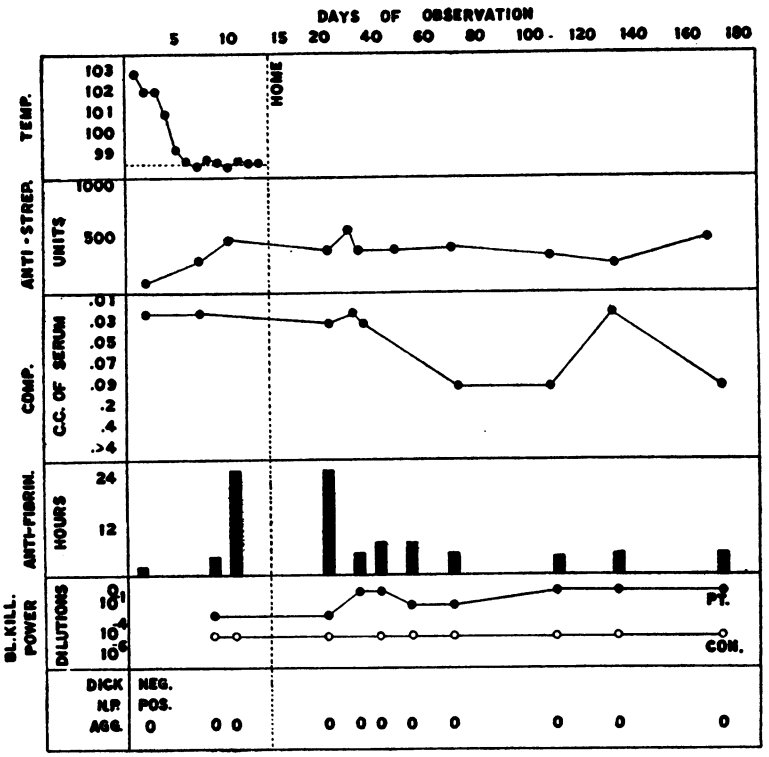

FIG. 8. CASE 2, SHOWING THE CHANGES IN THE VARIOUS SEROLOGICAL REACTIONS DURING AND FOLLOWING AN ATTACK OF ERYSIPELAS

Figure 9 illustrates the fact that erysipelas may occur in spite of the presence of increased resistance to fibrinolysis and good streptococcidal power of the whole blood. It is obvious that the blood of the control possessed as great a strepto-

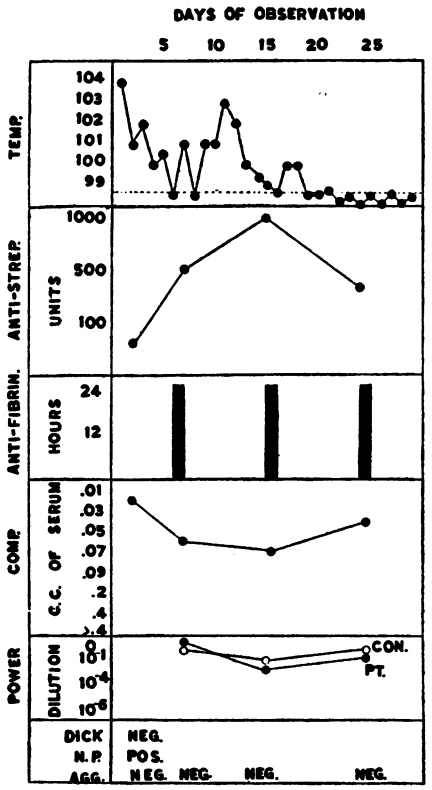

FIG. 9. CASE 3, SHOWING THE SEROLOGICAL REACTIONS DURING THE COURSE OF THE ILLNESS

coccidal power for the organism causing the disease as did the blood from the patient. This state of affairs was observed upon five occasions and emphasizes the fact that some individuals possess streptococcidal power of high degree against certain strains of hemolytic streptococci and still remain susceptible to local infections produced by such organisms.

To explain the recovery of erysipelas, it has been postulated that it is dependent upon: (1) the development of a local tissue immunity, and (2) a neutralization of toxin. These views require comment.

Local immunity. It has been postulated, especially by Gay and Rhodes (13), that there exists a true local tissue immunity following local streptococcus infection or immunization. This statement was based upon clinical and experimental observations. They pointed out that it had been shown in both man and in animals that the injection of hemolytic streptococci into an area of skin which had been the site of erysipelas some weeks before may not be followed by an infection. This applied not only to the previously involved area but also to other areas of skin as well. Working with rabbits, Gay and Rhodes reported that following recovery from erysipelas there was complete protection against intradermal reinoculation, irrespective of its locality, provided one waited for at least three weeks after the primary inoculation induced by previous intradermal infection or immunization could be associated with a lack of protection against intravenous injection of organisms. Conversely, intravenous immunization protected better against intravenous than against intradermal injection. From these observations, they concluded that a true local tissue immunity existed following the infection. It was inferred that the fixed tissue cells of the skin themselves had become immune to infection.

Rivers and Tillett (14) have demonstrated that dermal tissues of a rabbit become more refractory than normal skin to infection with hemolytic streptococci when they are infiltrated with normal serum, homologous serum or meat infusion broth, 24 hours before inoculation. Of the three substances, the most effective was the homologous immune serum. The refractory state induced in the tissues by the normal serum or the meat infusion broth was said to be non-specific in character, whereas the amount of resistance produced by the immune serum that was greater than that caused by the normal serum was considered to be the degree of local passive immunity conferred upon the tissues treated with the immune serum. It should be recalled that the tissues were more resistant to the infection when the inflammatory reaction had been induced *before* the inoculation of hemolytic streptococci. The precise mechanism by which this refractory state was brought into being remained obscure, but it was manifest that local passive immunity could be induced with homologous immune serum and existed long enough to prevent a local infection of the skin.

Amoss and Bliss (15) also reported that repeated injections of hemolytic streptococci in rabbits were followed by a demonstrable humoral immunity and, with the appearance of the antibodies, the skin became generally resistant to infection with hemolytic streptococci. It was found that the skin showed some resistance to repeated injection of microorganisms so that the reactions to second injections of the same microorganisms were not so striking as the first infections.

From the observations cited it is not absolutely clear that local immunity of the tissues can exist to the extent that bacteria are immobilized locally and their growth suppressed without the existence of humoral immunity. Indeed, from the experiments of Rich and McKee (16) with pneumococci, and others with different organisms, it would appear that fixation of organisms locally in the immune animal is dependent largely upon the presence of immune bodies in the blood serum of the animal, rather than upon immunity of the fixed tissue cells.

Neutralization of toxin. The evidence that a toxin is elaborated from the local lesion in erysipelas is controversial insofar as its presence has been detected in the circulating blood. Birkhaug (17) reports the finding of a soluble toxin in the circulating blood of patients with erysipelas, whereas Francis (18) was unable to confirm this observation. There is ample evidence, however, that many strains of hemolytic streptococci which are isolated from the lesions of erysipelas are capable of producing toxin.

Francis has reported, however, that early in the course of the disease there were antibodies in the circulating blood which were capable of neutralizing the toxic filtrates of hemolytic streptococci isolated from the lesions when such filtrates were tested on human skin. As the disease progressed, there was a tendency for patients to show increased reactivity of the skin to toxic filtrates of the organisms and a decrease in the ability of the serum to neutralize the toxic filtrate. The conclusions reported by Francis were to the effect that recovery from erysipelas in adults was not due to the neutralization of a circulating toxin through the development of an antitoxin, but it was related to the development of allergy to products of the growth and dissolution of streptococci in the erysipelatous lesion.

From the present studies, we have no comparable or direct evidence bearing upon the above question. We have found that 29 of the 30 patients gave no reaction to the Dick toxin and 26 of the 30 patients reacted in a positive manner to the nucleoprotein of a hemolytic streptococcus derived from scarlet fever and a strain which has a broad antigenic base (19). These reactions gave no indication regarding the mechanisms of recovery, but indicate that many patients with erysipelas are capable of neutralizing Dick toxin and react to the nucleoprotein of this organism (20) as do other individuals with hemolytic streptococcal infection.

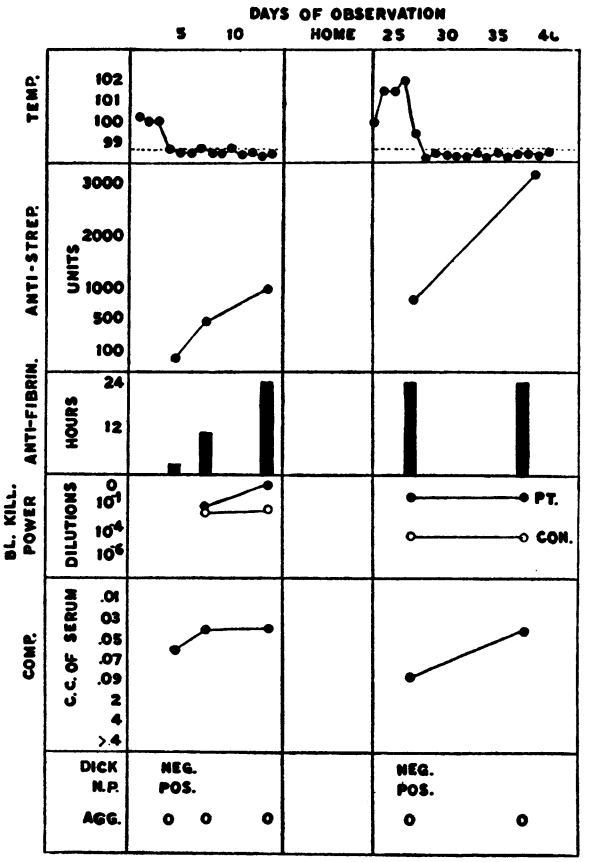

FIG. 10. CASE 10, SHOWING THE SEROLOGICAL REACTIONS IN TWO ATTACKS OF ERYSIPELAS

From our studies, there can be little question that during the course of erysipelas there is evidence of the appearance or increase of antibodies against the different special properties of the he-

molytic streptococcus. The intensity of the different responses varied from case to case and, in many, there was evidence of some humoral immunity early in the course of the disease. It is not inconsistent, then, to say that the presence of some resistance to infection as measured by streptococcidal power, may not protect against a local lesion provided the conditions for infection are favorable; once the infection becomes established there is frequently an increase in humoral immunity which may aid in recovery.

Recurrent attacks. It is a matter of common experience to observe repeated attacks of erysipelas in the same individual. It would appear that one attack of erysipelas renders some individuals more susceptible rather than more resistant to subsequent infections, and, from our studies and those of others (21, 22, 23, 24, 25), there can be little doubt that this is the case.

lesion on both occasions; the clinical course was similar, and the second attack occurred in spite of the presence of the different antibodies above the normal level.

The second type is illustrated in Figure 11. This patient has had, to our knowledge, eight attacks of erysipelas during the past two years, six attacks of facial erysipelas and two attacks of erysipelas of the legs. The attacks are abrupt in onset, and within a few hours the local lesion often, but not always, reaches its maximum intensity. Microorganisms cannot be isolated from the lesions themselves, but they are present constantly in the paranasal sinuses and the nasal secretions. Moreover, attacks can be induced by the injection of a toxic filtrate derived from the organisms that are present in the nasal secretions. In view of the repeated attacks, the inability to obtain organisms from the lesions, and the pro-

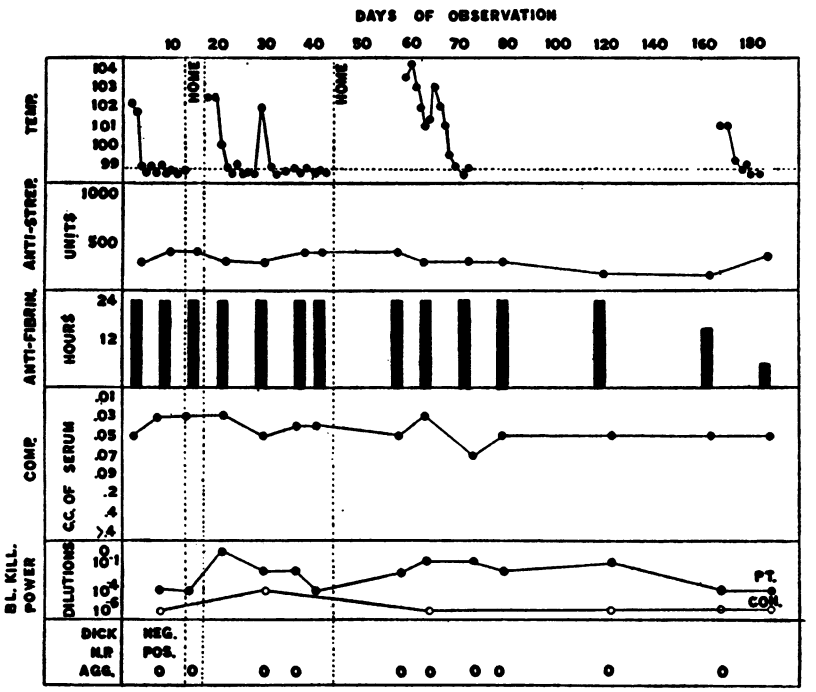

FIG. 11. CASE 1, SHOWING THE SEROLOGICAL REACTIONS DURING AND BETWEEN REPEATED ATTACKS OF ERYSIPELAS

We have observed recurrent attacks of erysipelas of several types. The first is illustrated in Figure 10. In this case, the two attacks of erysipelas occurred within two weeks of each other, and hemolytic streptococci were isolated from the

duction of a typical attack by the injection of a toxic filtrate into a site some distance from the area which becomes involved, there seems to be little doubt that this type of reaction is due to a response of sensitized tissues to the products of

the hemolytic streptococcus. Figure 11 shows that the repeated attacks of erysipelas occurred in spite of the fact that there was a certain degree of resistance to streptococcal infection as evidenced by the amounts of the different antibodies.

SUMMARY AND CONCLUSIONS

From a study of the clinical course of 30 patients with erysipelas and the serological reactions that can be demonstrated during and following the disease, the following results were obtained.

1. Erysipelas not infrequently follows a streptococcal infection of the throat and nasal passages.

2. The antistreptolysin (antihemolysin) of the blood serum increased during the course of the disease, and frequently remained above the original titer for periods of 40 days to six months. The highest titer was usually reached within the first 20 days after the onset of the illness.

3. Twenty-four of the 30 patients developed maximum resistance of fibrinolysin within the five to fourteen days of the illness. Once it appeared, it persisted for periods of time varying from 8 to 150 days. While there was no precise correlation between the appearance of maximum resistance and recovery, we considered this reaction a response on the part of the host to streptococcal infection.

4. The streptococcidal power of the blood showed that during the course of the disease there may be an increase in the titer of this property of the blood or it may remain stationary. Increases in killing power could not be correlated with recovery. It was considered to be a response on the part of the host to the streptococcal infection.

5. The complement titer of the blood serum was determined, and it was found that it increased more than 0.1 cc. in five, decreased more than 0.1 cc. in nine, and remained the same in 16. Generally speaking, there was an adequate amount of complement present for phagocytosis.

6. Only one of the 30 patients reacted positively to Dick toxin, whereas 24 patients showed positive reactions to 0.1 mgm. of the nucleoprotein of hemolytic streptococcus.

7. Three patients developed agglutinins against their own organisms in titers varying from 1 to 40 to 1 to 80. In two of these, there were suppurative complications.

8. The mechanism of recovery from erysipelas is discussed in the light of the above findings.

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